EXPLORING NICKEL- AND IRON- CATALYZED CYCLOADDITION ROUTES TO *N*- HETEROCYCLES

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Transition metal catalyzed [2+2+2] cycloaddition reactions are an important class of reactions that provide the means for the rapid construction of various carbocyclic and heterocyclic compounds. Over the past several years, our efforts have been focused on exploring metal catalyzed cycloaddition reactions to find new methods and improve existing methods to access heterocyclic core structures such as pyridines, pyridones and pyrimidones.

Enynes and isocyanates in the presence of a nickel-based catalyst system undergoes cycloaddition affording *E*- and the *Z*-dienamides in moderate to good yields with the *E*-dienamide being the major product. The substrate scope with respect to isocyanate and enyne structures was also determined. It was observed that aryl as well as alkyl isocyanates undergo this cycloaddition reaction. Internal enynes afforded the dienamide products while terminal enynes afforded lactams.

A new catalytic system involving iron acetate and a sterically hindered bis(aldimino)pyridyl ligand was also developed. This Fe-complex catalyzed the cycloaddition reaction of alkynenitriles and alkynes to afford pyridines in moderate to good yields. Symmetrical and unsymmetrical exogenous alkynes can be used in this cycloaddition reaction. Alkyl, aryl, and terminal alkynenitrile afford good yields of the

pyridine products. Five- and six-membered fused pyridines can be synthesized in good yields by this methodology.

The synthesis of 2-aminopyridines by the cycloaddition reaction of diynes and cyanamides in the presence of an iron catalyst system has also been studied. The Fe-catalytic system is a combination of iron chloride and a bis(aldimino)pyridyl ligand and it leads to good to excellent yields of desired product. Five- and six-membered fused 2-aminopyridines were prepared in good yields by utilizing this methodology. Various *N*-alkyl-alkyl, *N*-aryl-aryl, and *N*-alkyl-aryl cyanamides undergo this cycloaddition reaction with diynes to afford 2-aminopyridines in good yields.

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LIST OF ABBREVIATIONS

Ac- acetyl

acac – acetylacetone

BINAP – 2,2’ – bis(diphenylphoshino)-1,1’-binaphtyl

Bn – benzyl

Boc – *tert*–butyl carbamate

COD – cyclooctadiene

Cy – cyclohexyl

d – doublet

dba – trans, trans – dibenzylideneacetone

DIAD – diisopropylazodicarboxylate

DMF – *N, N* - dimethylformamide

DMA – *N, N* – dimethylacetamide

dppe – 1,2- Bis(diphenylphosphino)ethane

dppf – diphenylphosphinoethane

Et – ethyl

I*t*Bu – 1,3-di-*tert*-butylimidazol-2-ylidene

IMes – 1,3-bis-(2,4,6-trimethylphenyl)-imidazol-2-ylidene

IPr – 1,3-bis-(2,6-diisopropylphenyl)-imidazol-2-ylidene

iPr – iso-propyl

M- metal

m – multiplet

MeCN – acetonitrile

NBS – *N*-bromosuccinimide

n-Bu – normal-butyl

NHC – *N*-heterocyclic carbene

$Ni(COD)_2$ – Bis(1,5-cyclooctadiene)nickel

NMR – nuclear magnetic resonance

$PnBu_3$ – tri(n-butyl)phosphine

PCy_3 – tricyclohexylphosphine

Ph – phenyl

PPh_3 – triphenylphosphine

q – quartet

s – singlet

SIPr – 1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene

t – triplet

THF- tetrahydrofuran

TMS- trimethylsilyl

X - halogen

CHAPTER 1

METAL CATALYZED CYCLOADDITION REACTIONS- AN INTRODUCTION

Heterocycles are prevalent in various natural products and pharmaceutically active compounds.[1] Among various methodologies, transition metal-catalyzed methodologies have played an important role in the synthesis of carbo- and heterocyclic compounds.[2] Of the many transition metal-catalyzed synthetic methods used for the preparation of cyclic compounds, the [2+2+2] cycloaddition reactions are of significant importance. Examples of [2+2+2] cycloaddition reactions involve the reaction of three alkyne moieties to form benzene derivatives, or the reaction of a diyne with an alkene group to form a cyclohexadiene core. It is noteworthy that unsaturated systems used in cycloaddition reactions could be heteroatomic (e.g., isocyanates, nitriles, carbon dioxide etc.). These reactions involving the use of heteroatomic unsaturated moieties lead to the formation of heterocyclic compounds such as pyridine, pyrimidone, cyanamide, and pyrans.

The [2+2+2] cycloaddition reactions[2a] could be classified into three types based on the location of the unsaturated used in the substrate:

a) Intermolecular: three unsaturated systems present in three different molecules undergo cycloaddition (Figure 1.1, Equation 1.1). b) Partially intermolecular: two unsaturated functionalities of the same molecule undergo cycloaddition with another unsatuared molecule (Figure 1.1, Equation 1.2). c) Intramolecular: all three unsaturated functionalities are present in the same molecule (Figure 1.1, Equation 1.3).

Typically, cycloaddition reactions involve the formation and cleavage of multiple bonds in a concerted manner to form cyclic compounds. In these reactions, all the atoms of the starting materials are retained in the product. Thus, the [2+2+2] cycloaddition methodology is an elegant and atom efficient synthetic approach to cyclic compounds. Utilization of this unique methodology affords heterocycles from relatively simple starting materials.

Before we go into the details of the cycloaddition reactions, it is important to understand the possible mechanistic pathways[2b] of product formation. A simple representation of the [2+2+2] cycloaddition reactions is shown in Figure 1.2. For simplicity, the reaction of an internal diyne and a generic isocyanate as the heteroatomic unsaturated system coupling partner is discussed. Initial oxidative coupling of an alkyne moiety and an isocyanate (Figure 1.2, pathway A) in the presence of a transition metal is followed by the insertion of the second alkyne moiety between the metal-carbon bond results in the formation of a seven membered metallacycle. An alternative mechanism involves the oxidative coupling of the alkyne moieties that is followed by the insertion of the isocyanate moiety (Figure 1.2, pathway B). This would result in the formation of the same seven membered metallacycle. Reductive elimination of the metal from the seven membered metallacycle would afford the corresponding cycloaddition product. The

reaction mechanism may vary depending on the metal and substrates used in the cycloaddition reaction.

This chapter will provide a background on the [2+2+2] cycloaddition reaction of alkynes and various Ni-based heterocumulenes for the synthesis of pyridones and pyridines. It has been divided into the following sections based on the product formed and further subdivided based on the type of metal catalyst used in the reaction:

I) [2+2+2] Cycloaddition of alkynes and isocyanates to synthesize pyridones using cobalt, nickel, ruthenium, and rhodium

II) [2+2+2] Cycloaddition of alkynes and nitriles to synthesize pyridines using cobalt, rhodium, ruthenium, nickel/zirconium, titanium, tantalum, and iron.

[2+2+2] Cycloaddition reactions of alkynes and isocyanates to synthesize pyridones

Pyridones can be constructed by the reaction of alkynes and isocyanates in the presence of a suitable transition metal catalyst. Isocyanates are easily accessible via the Curtius rearrangement.[3] Similarly, diversely substituted alkynes[2] are easily accessible and hence useful coupling partners in cycloaddition reactions.

Application of cobalt based catalysts

Yamazaki[4a] reported the first synthesis of pyridones using cycloaddition chemistry by reacting alkynes and isocyanates in the presence of catalytic amounts of a cobalt based catalyst (Equation 1.4). To access differently substituted pyridones, Vollhardt[4b] tethered

an alkyne and an isocyanate functionality and reacted the alkynyl-isocyanates with various alkyne substrates in the presence of a cobalt-catalyst to yield pyridones at elevated temperatures (130 °C) (Equation 1.5). Bicyclic pyridones containing a macrocycle can be prepared in good yields by reacting diynes and isocyanates (Equation 1.6) as demonstrated by Marynoff.[4c] However, a large excess of the isocyanate is required for the cycloaddition reaction.

Application of nickel/zirconium based catalysts

Hoberg[5a-c] was the first to demonstrate the use of nickel in the synthesis of pyridones. Selective pyridone formation in the reaction of an alkyne **1** with an isocyanate in the presence of a stoichiometric amount of nickel (Scheme 1.1) was reported. Nickelacyclopentenone **2** was isolated by the oxidative coupling of alkyne **1** and phenyl isocyanate and was then coupled with one more equivalent of an alkyne functionality to afford the pyridone in moderate yields via nickelacycle **3**. Although this was the first successful protocol to prepare pyridones using nickel, the process to prepare the nickelacycle required low temperatures (-50 °C) and long reaction time (3 days). The synthesis of pyridones has been reported by Louie[5d,e] by using metal complexes as catalysts. Using a Ni/SIPr (1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene) catalytic system, pyridones can be prepared in high yields at ambient temperature by the reaction of diynes and isocyanates (Equations 1.7 and 1.8). Using the same Ni/NHC catalytic system, the synthesis of pyrimidines was also achieved in moderate to good yields by the reaction of two equivalents of isocyanate and one equivalent of alkyne

(Equation 1.9). It was observed that both activated and unactivated isocyanates provided the desired cycloaddition products.

Application of ruthenium based catalysts

Using a ruthenium-based catalyst, Itoh[6] reported the synthesis of pyridones by the reaction of 1,6-diynes and isocyanates (Equation 1.10). The reaction afforded pyridones in good yields in the presence of activated isocyanates.

Application of rhodium based catalysts

Tanaka[7] synthesized pyridones and axially chiral pyridones by reacting diynes and isocyanates in good yields using a cationic rhodium catalyst (Equations 1.11 and 1.12).

In all these cycloadditon reactions discussed so far, pyridones were synthesized by the cycloaddition of alkynes or diynes and isocyanates. If one of the alkyne moieties were to be substituted for an alkene, the product thus formed would be a lactam. Lactams are structurally important and present in highly significant biologically active compounds.[8] Rovis demonstrated that in the presence of a rhodium catalyst,[9a] cyclization of an alkenyl-isocyanate and an alkyne afforded a vinylogous amide and lactam products (Equation 1.13). High selectivity of >20:1 was observed favoring the vinylogous amide product. This methodology was also extended to access structural cores of lasubine alkaloids. Matsubara[9c] used a combination of nickel cyclooctadiene and IPr [1,3-bis-(2,6-diisopropylphenyl)-imidazol-2-ylidene] catalyzed cycloaddition reaction of alkynes,

acrylates, and isocyanates affording two regioisomers of γ-butyrolactams in moderate regioselectivity and yields (Equation 1.14).

[2+2+2] Cycloaddition of Alkynes and Nitriles for the Synthesis of Pyridines

Pyridine rings are omnipresent in various natural products and bioactive compounds.[1a] Transition metal catalysts have been used extensively to construct pyridine rings via the [2+2+2] cycloaddition reaction.

Application of cobalt based catalysts

Cobalt based catalysts has by far dominated the field of cycloaddition chemistry. Bönnenman[10a] was among the first to demonstrate the use of cobalt in cycloaddition reactions of alkynes and activated nitriles (Equation 1.15). Pyridines can be also be synthesized by the cycloaddition reaction of alkynenitriles and exogenous alkynes in the presence of $CoCp(CO)_2$ as demonstrated by Vollhardt[10b] (Equation 1.16). However, the catalytic system required high temperatures and photolytic conditions for catalyst activation. Eaton[10c] developed a water-soluble cobalt catalyst system which afforded pyridines in good yields (Equation 1.17).

Application of rhodium based catalysts

The earliest example of the use of rhodium in the preparation of pyridines by cycloaddition reactions was demonstrated by Ingrossio[11a] wherein $RhCp(C_2H_4)_2$ used in the cycloaddition of 1-hexyne and propionitrile. By this method, pyridine products were obtained albeit in moderate yields in an almost equal mixture of regioisomers. By switching to $RhCp^*(C_2H_4)_2$ the yield of the pyridine[11b] products increased to 67 %. However, high reaction temperatures were necessary for the cycloaddition reaction. Tanaka[11c] demonstrated pyridines can be prepared with only 3 mol % rhodium based catalyst by reacting diynes with nitriles. The yields of the pyridine product were quantitative when activated nitriles were used. However, the yields dropped significantly when unactivated nitriles were used in the cycloadddition reaction. In another example, reacting activated aryl ethynyl ethers with nitriles catalyzed by rhodium[11d] to yield the pyridine product as a single regioisomer.

Application of ruthenium based catalysts

Itoh[12a] was the first to synthesize pyridines using a ruthenium based catalyst (Equation 1.22). Diynes and dicyanides reacted to afford only one regioisomer of the pyridine product in good yields. Modification of the ruthenium catalyst to Cp^*RuCl[12b] (Equation 1.23) synthesized pyridines in excellent yields with low catalyst loading. However, slight excess of nitriles is required for the cycloaddition reaction. Saa[12c] used a cationic Ru based catayst (Equation 1.23) in the presence of NEt_4Cl to obtain good yields of the pyridine product from the reaction of diynes and dicyanides.

Application of nickel/zirconium based catalysts

Takahashi[13a] synthesized pyridines by an intermolecular cycloaddition between two different alkynes and a nitrile (Equation 1.25). The alkyne and the isocyanate were coupled with zirconium (Zr) to form an azazirconacyclopentenone. Then $Ni(PPh_3)_2Cl_2$ reacted with the azazirconacyclopentenone to form the nickelcyclopentenone. Insertion of the second alkyne affords the pyridine. This marked the first report of the use of nickel in the synthesis of pyridines. Unfortunately in this method stoichiometric amounts of both Ni and Zr were needed for this reaction. Louie[13b] successfully demonstrated that stoichiometric amounts of nickel were not needed to synthesize pyridines (Equation 1.26). Employing a combination of nickel and an *N*-heterocyclic carbene, IPr, pyridines were prepared in excellent yields with both unactivated nitriles at room temperature. This reaction can be carried out in an intermolecular fashion by combining alkynes and nitriles (Equation 1.27).[13c]

Applications of titanium based catalysts

Cycloaddition reactions are not entirely dependent on late transition metals for catalysis. Early transition metals such as titanium[14] have also been used in the synthesis of pyridines (Equation 1.28). Although, the reaction for some alkynes are high yielding, stoichiometric amounts of titanium are required for the cycloaddition reaction.

Application of tantalum based catalysts

Tantalum[15] has been used in the cycloaddition reaction of alkynenitriles and alkynes (Equation 1.29). However, this cycloaddition reaction has been applied to only one substrate and the reaction is stoichiometric in tantalum hexachloride.

Applications of iron based catalysts

Iron has also been used in the past for the preparation of pyridine. The very first example was reported by Sir William Ramsay[16a,b] in 1876. He synthesized pyridine in traces by passing hydrocyanic acid and acetylene through a red hot iron tube. Knoch[16c] prepared pyridine derivatives from the cycloaddition of alkynes and nitriles using an iron-phosphoranecyclooctadiene complex (Equation 1.30). Although the cycloaddition reaction required low catalyst loading, the desired pyridine product and alkyne cyclotrimerization products were obtained. By designing an iron-pentamethyl(cyclopentadienyl)acetonitrile sandwich complex, Ferré[16d] successfully afforded pyridine product in 73 % yield (Equation 1.31). However, this cycloaddition reaction required stoichiometric amounts of the iron-complex and was limited to one activated alkyne.

The above examples demonstrate the importance of the use of transition metal catalysts in the [2+2+2] cycloaddition reactions. It is clear that a variety of reactions with diverse substrates and catalysts have been developed and reported. However, certain deficiencies exist in our understanding and application of cycloaddition reactions. One example is the lack of a reaction protocol that combines readily accessible substrates

such as enynes and isocyanates. Therefore, developing such a cycloaddition reaction that could utilize the reactivity of an enyne and an isocyanate would be an interesting study. This study was undertaken in the Louie lab and the results obtained in the investigation using a nickel catalyst are discussed in Chapter 2.

The pyridine ring is an important structural motif. Although various metals catalyst have been developed to synthesize pyridine rings, very little work has been done in the application of iron based catalysis in these cycloaddition reactions. Iron is an interesting candidate for cycloaddition catalysts because it is less-toxic, relatively inexpensive, and readily available. Therefore, a study involving the use of Fe-catalysts in cycloaddition reactions was undertaken and the results have been discussed in Chapters 3 and 4. Chapter 3 provides the details of Fe-catalyzed synthesis of pyridine derivatives, whereas chapter 4 provides the details of Fe-catalyzed synthesis of 2-aminopyridine derivatives.

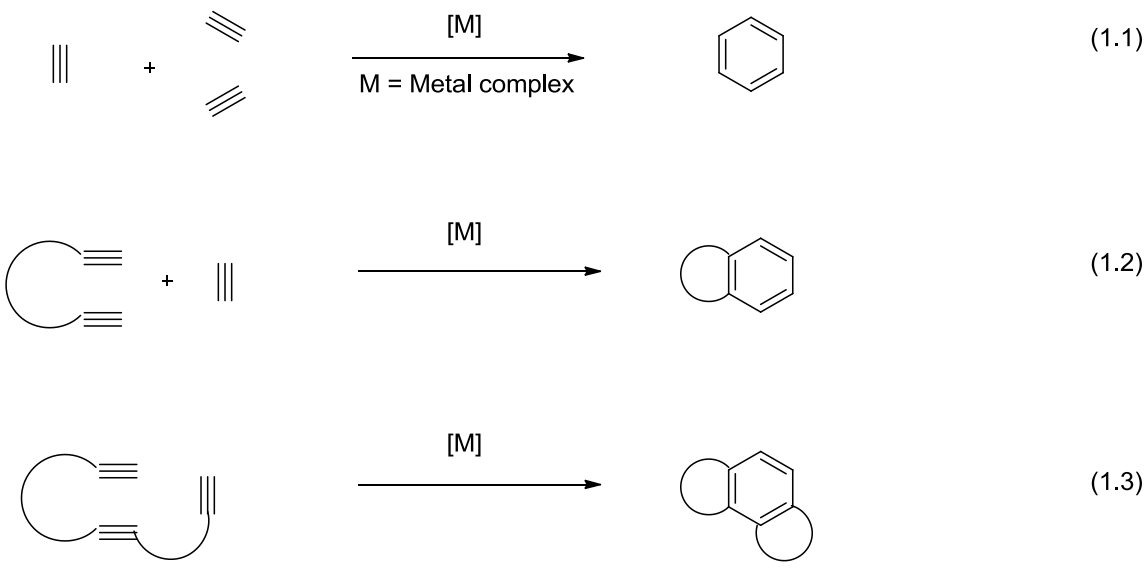


Figure 1.1 [2+2+2] Types of cycloaddition reactions (equations1.1-1.3)

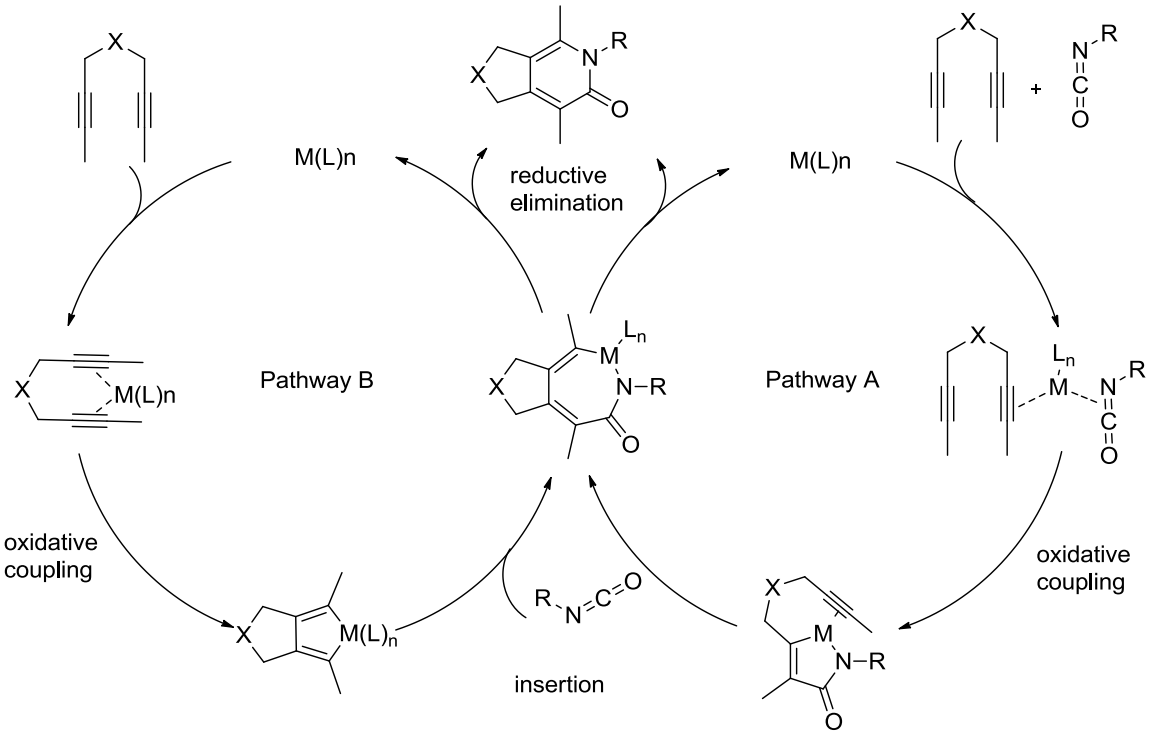
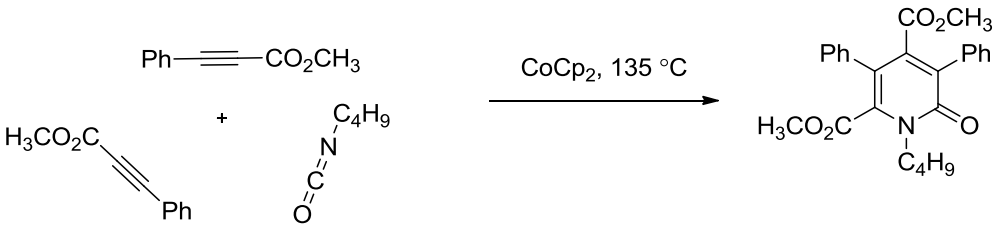
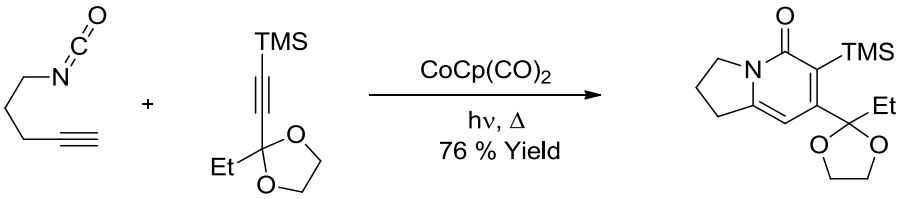


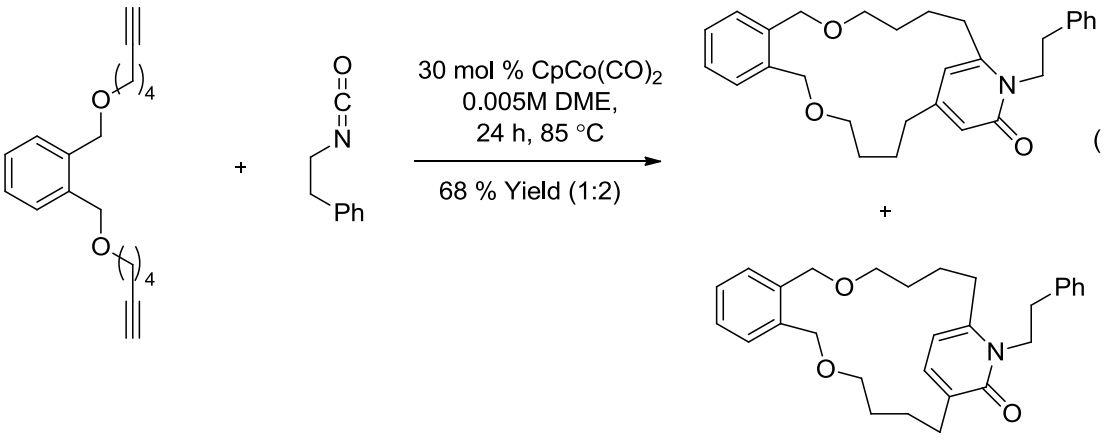
Figure 1.2 A [2+2+2] cycloaddition reaction between a diyne and an isocyanate


Ph
CO2CH3
H3CO2C
Ph
C4H9
N
C
O
CoCp2, 135 °C
CO2CH3
Ph
Ph
H3CO2C
N
O
C4H9

(1.4)

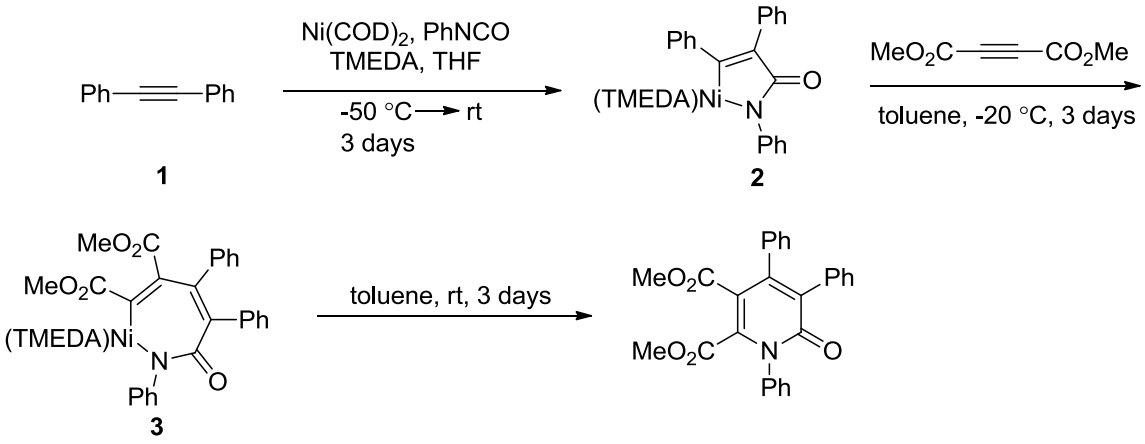

O
N
C
O
TMS
Et
O
O
CoCp(CO)2
hν, Δ
76 % Yield
O
N
TMS
Et
O
O

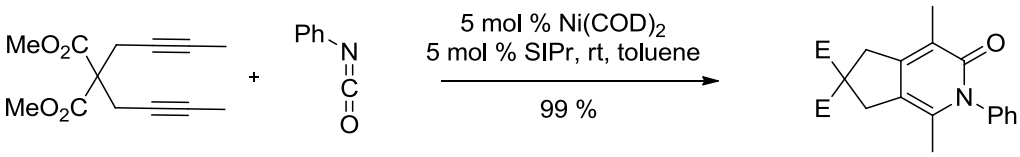
(1.5)


O
4
O
4
O
C
N
Ph
30 mol % CpCo(CO)2
0.005M DME,
24 h, 85 °C
68 % Yield (1:2)
O
O
N
Ph
O
+
O
O
N
Ph
O

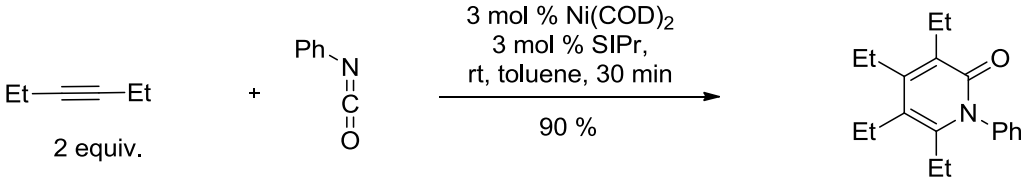
(1.6)

Scheme 1.1 Hoberg's synthesis of pyridones using nickel

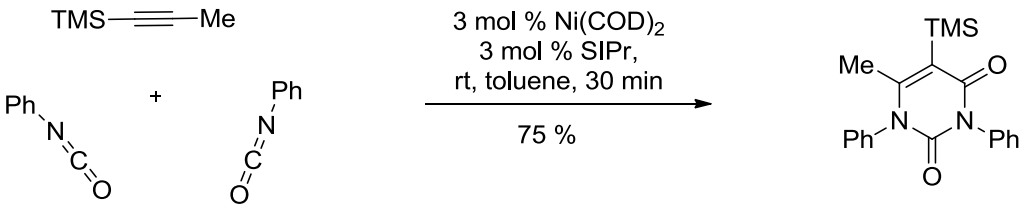



MeO2C
MeO2C
Ph
N
C
O
5 mol % Ni(COD)2
5 mol % SIPr, rt, toluene
99 %
E
E
O
N
Ph

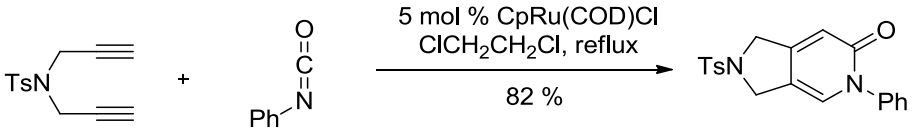
(1.7)


Et
Et
2 equiv.
Ph
N
C
O
3 mol % Ni(COD)2
3 mol % SIPr,
rt, toluene, 30 min
90 %
Et
Et
O
Et
N
Ph
Et

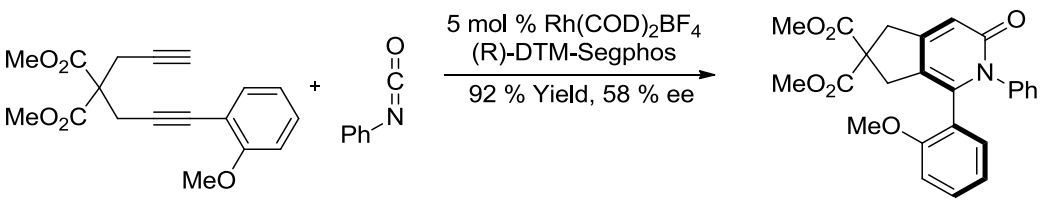
(1.8)


TMS
Me
Ph
N
C
O
Ph
N
C
O
3 mol % Ni(COD)2
3 mol % SIPr,
rt, toluene, 30 min
75 %
TMS
Me
O
N
N
Ph
Ph
O

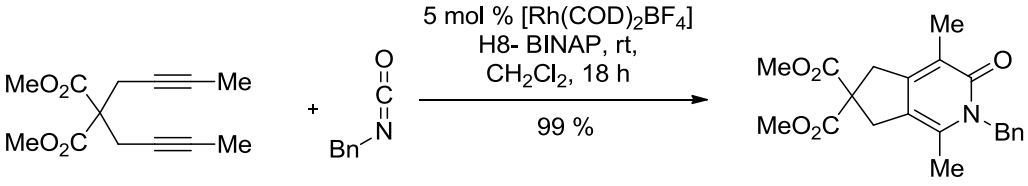
(1.9)


5 mol % CpRu(COD)Cl
ClCH2CH2Cl, reflux
82 %
TsN
Ph
O
N
Ph

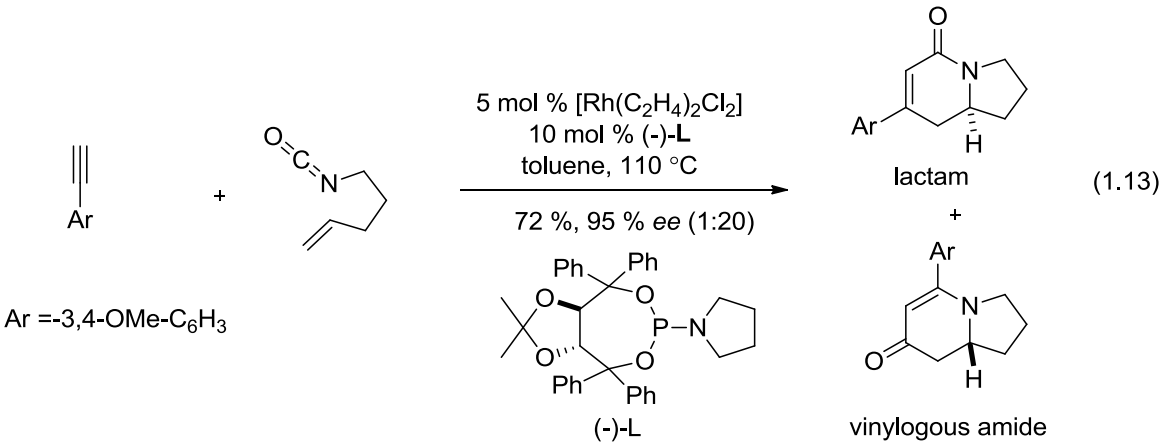
(1.10)


5 mol % Rh(COD)2BF4
(R)-DTM-Segphos
92 % Yield, 58 % ee
MeO2C
MeO2C
MeO
Ph
MeO
O
N
Ph

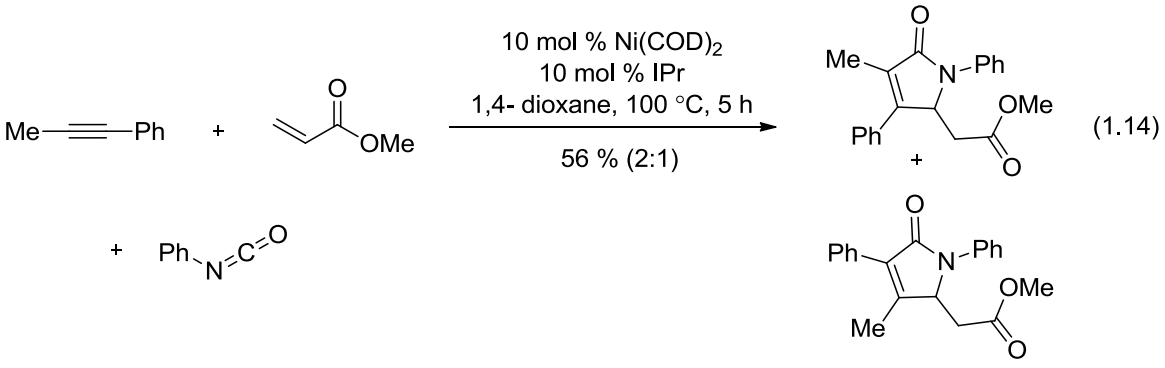
(1.11)


5 mol % [Rh(COD)2BF4]
H8- BINAP, rt,
CH2Cl2, 18 h
99 %
MeO2C
MeO2C
Me
Me
Bn
Me
MeO2C
MeO2C
Me
O
N
Bn
Me

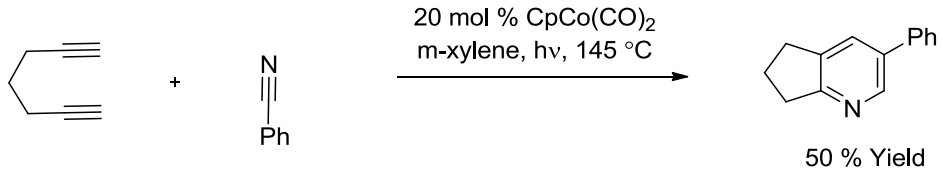
(1.12)


5 mol % [Rh(C2H4)2Cl2]
10 mol % (-)-L
toluene, 110 °C
72 %, 95 % ee (1:20)
Ar
Ar =-3,4-OMe-C6H3
Ph
Ph
O
P–N
(-)-L
lactam
+
vinylogous amide

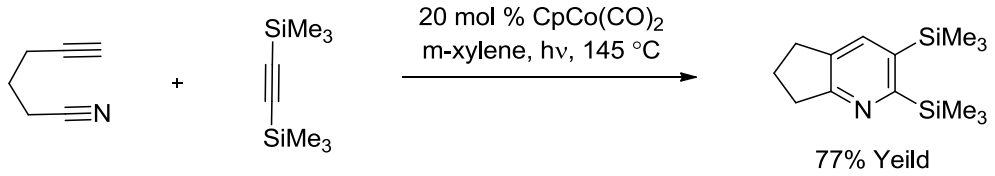
(1.13)


10 mol % Ni(COD)2
10 mol % IPr
1,4- dioxane, 100 °C, 5 h
56 % (2:1)
Me
Ph
OMe
+
Ph–N=C=O

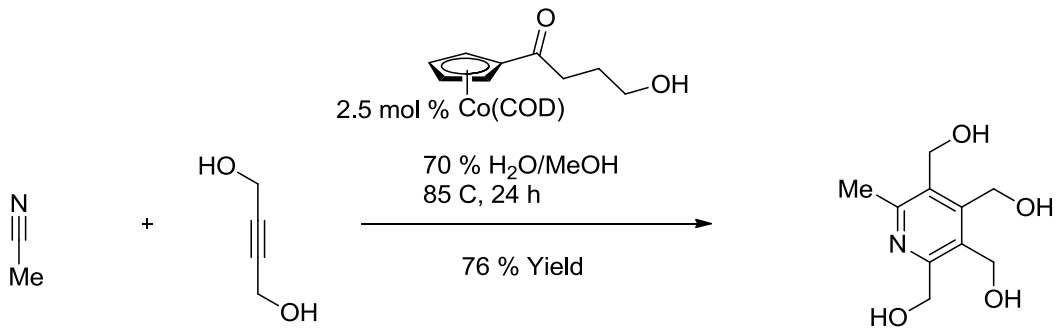
(1.14)


20 mol % CpCo(CO)2
m-xylene, hν, 145 °C
N
Ph
Ph
N
50 % Yield

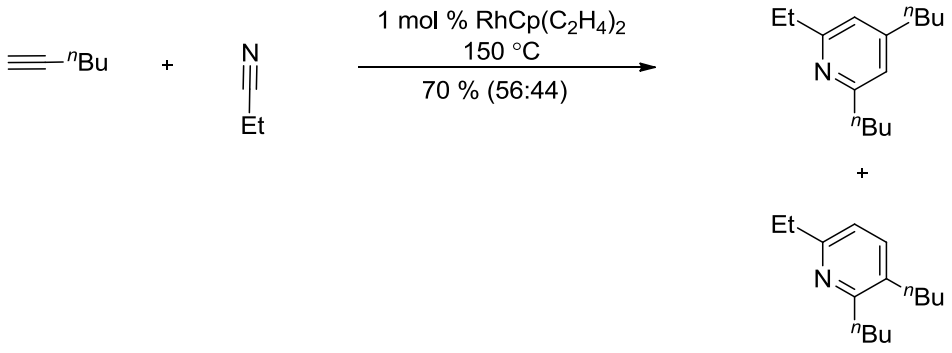
(1.15)


SiMe3
20 mol % CpCo(CO)2
m-xylene, hν, 145 °C
N
SiMe3
SiMe3
N
SiMe3
77% Yeild

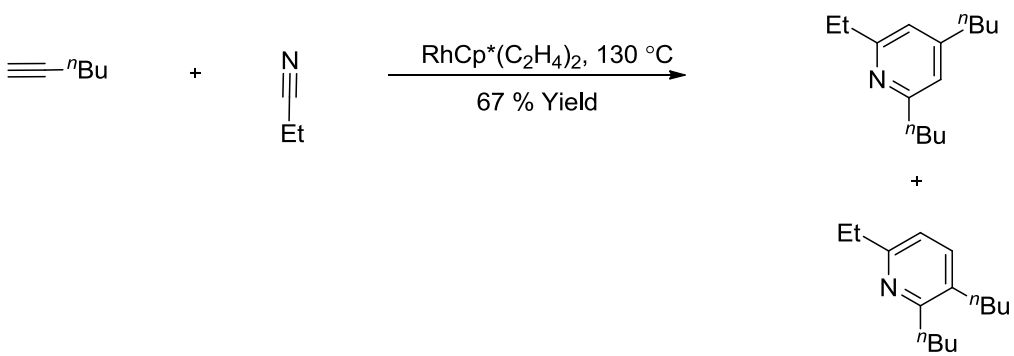
(1.16)


O
OH
2.5 mol % Co(COD)
70 % H2O/MeOH
85 C, 24 h
76 % Yield
N
Me
HO
OH
OH
Me
N
OH
OH
HO

(1.17)


1 mol % RhCp(C2H4)2
150 °C
70 % (56:44)

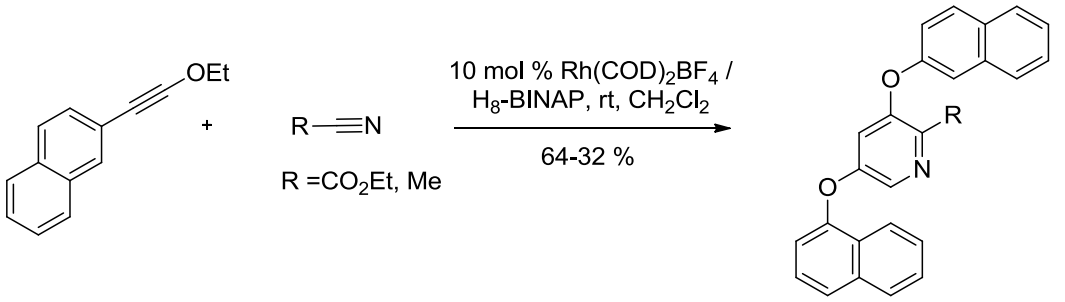
(1.18)


RhCp*(C2H4)2, 130 °C
67 % Yield

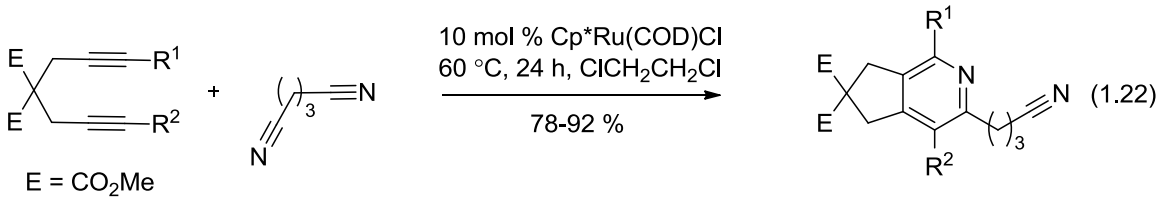
(1.19)


2 mol % Rh(COD)2BF4 /
BINAP, rt, CH2Cl2
63-99 %
R =CO2Et, Me
E = CO2Me

(1.20)

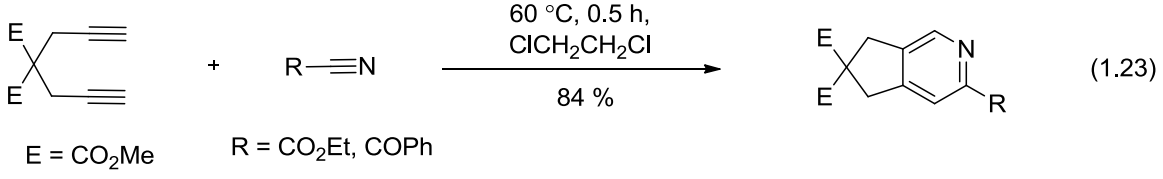


(1.21)

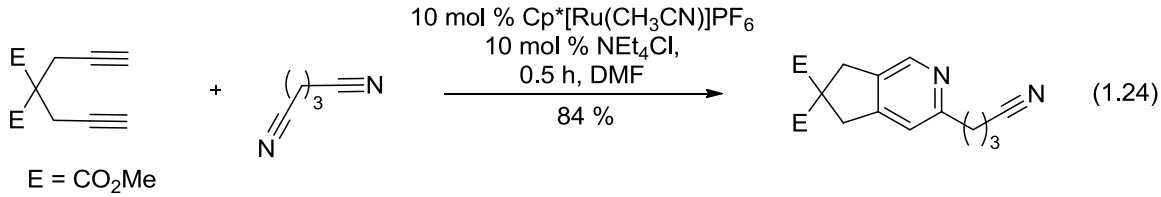


(1.22)

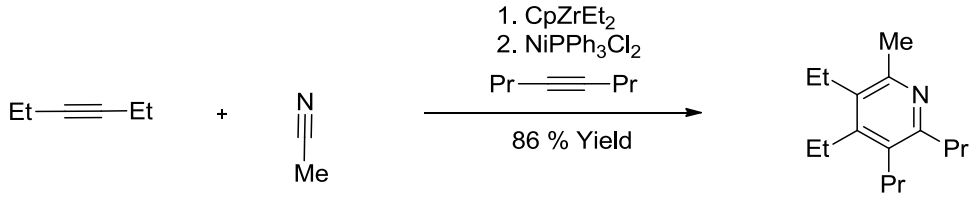
R^1 = Ph, R^2 = H
R^1= TMS, R^2 = H



(1.23)

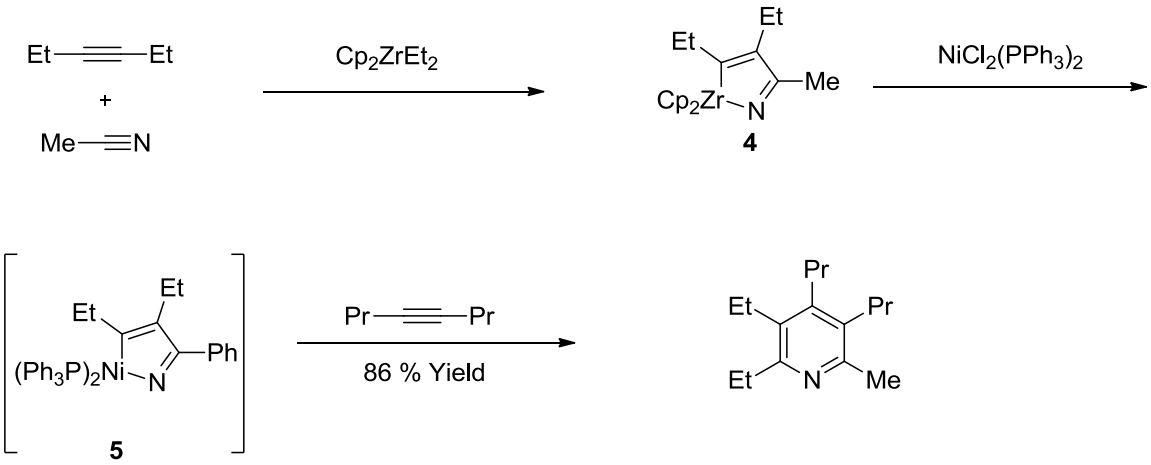

10 mol % Cp*[Ru(CH3CN)]PF6
10 mol % NEt4Cl,
0.5 h, DMF
84 %
E = CO2Me

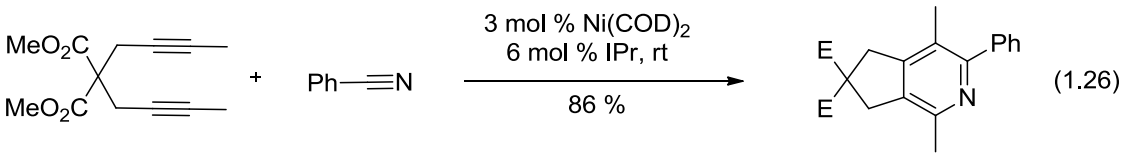
(1.24)


1. CpZrEt2
2. NiPPh3Cl2
Pr—≡—Pr
86 % Yield

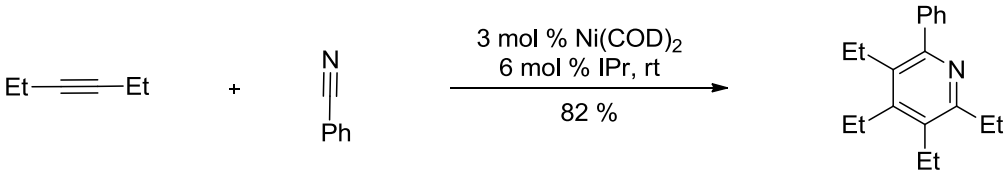
(1.25)

Scheme 1.2 Pyridine synthesis using stoichiometric amounts of zirconium and nickel

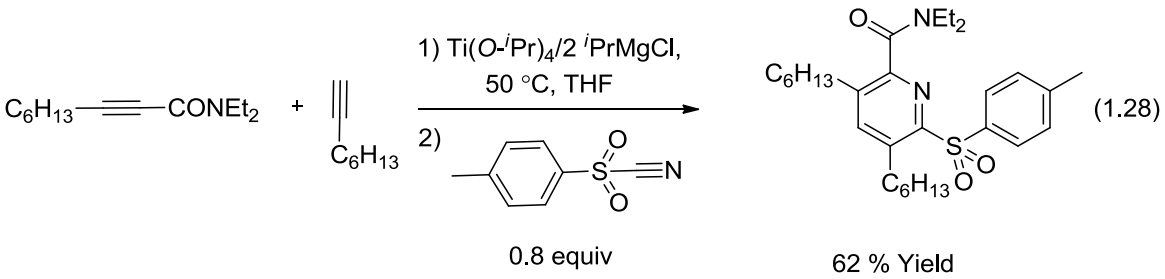




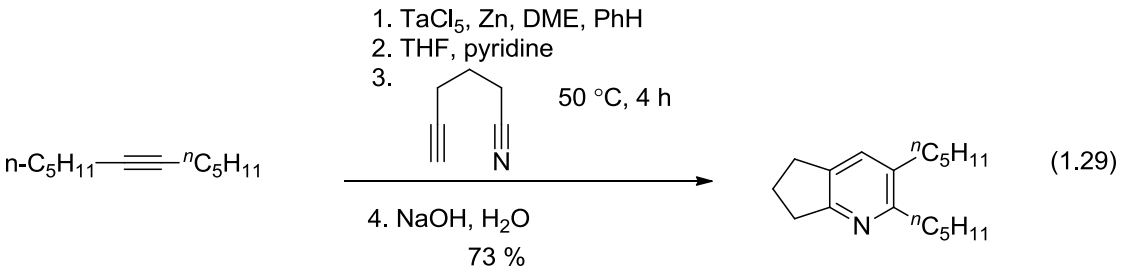
(1.26)


Et
Et
+
N
Ph
3 mol % Ni(COD)2
6 mol % IPr, rt
82 %
Ph
Et
N
Et
Et
Et

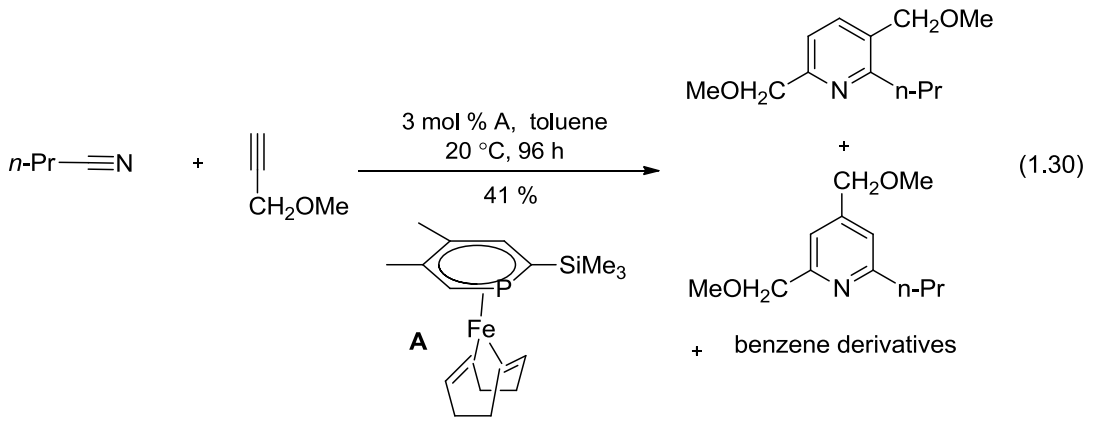
(1.27)


C6H13
CONEt2
+
C6H13
1) Ti(O-iPr)4/2 iPrMgCl,
50 °C, THF
2)
O
S
N
O
0.8 equiv
O
NEt2
C6H13
N
S
O
C6H13
O
62 % Yield

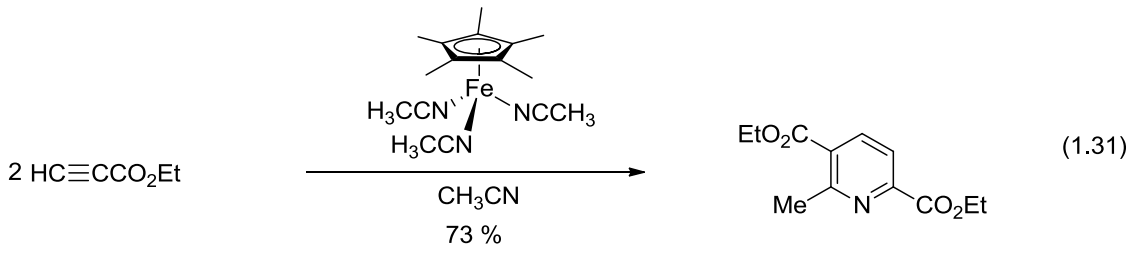
(1.28)


n-C5H11
nC5H11
1. TaCl5, Zn, DME, PhH
2. THF, pyridine
3.
N
50 °C, 4 h
4. NaOH, H2O
73 %
nC5H11
N
nC5H11

(1.29)


n-Pr—≡N
+
CH2OMe
3 mol % A, toluene
20 °C, 96 h
41 %
SiMe3
P
Fe
A
CH2OMe
MeOH2C
N
n-Pr
+
CH2OMe
MeOH2C
N
n-Pr
+ benzene derivatives

(1.30)


2 HC≡CCO2Et
Fe
H3CCN
NCCH3
H3CCN
CH3CN
73 %
EtO2C
Me
N
CO2Et

(1.31)

References

1. a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell:Oxford, **2000**. b) Romeo, G.; Chiacchigo, U.; Merino, P. *Chem. Rev.* **2010**, *110*, 3337-3370. c) Kollár, L.; Keglevish, G.; *Chem. Rev.* **2010**, *110*, 4257-4302.

2. Reviews of cycloaddition; a) S. Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. b) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. c) Chopade, P.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. d) Schore, N. *Chem. Rev.* **1988**, *88*, 1081. e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, 104, 2127. f) Varela, J. A.; Saá, C. *Synlett.* **2008**, 2571

3. Synthesis of isocyanates and their reactions: a) Braunstein, P.; Nobel, D. *Chem. Rev.* **1989**, *89*, 1927. b) Ozaki, S. *Chem. Rev.* **1972**, *72*, 457.

4. Cobalt catalyzed: a) Hong, P.; Yamazaki, H. *Tetrahedron Lett.* **1977**, 1333. b) Earl, R. A.; Vollhardt, K. P. C.; *J. Org. Chem.* **1984**, *49*, 4786. c) Boñaga, L. V. R.; Zhang, H-C.; Moretto, A. F.; Ye, H.; Gauthier, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473.

5. Nickel catalyzed: a) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*-235. b) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324. c) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, *252*, 359. d) Duong, H. A.; Cross, M. J. Louie, *J. Am. Chem. Soc.* **2004**, *126*, 11438–11439. e) Duong, H. A.; Louie, J. *Tetrahedron* **2006**, *62*, 7552.

6. Ru catalyzed: a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117.

7. Rh catalyzed: a) Tanaka, K.; Wada, A.; Noguchi, K. *Org. Lett.* **2006**, *8*, 907. b) Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T. *Tetrahedron Lett.* **2006**, *47*, 7107.

8. a) Williams, R.; Manka, J. T.; Rodriguez, A. L.; Vinson, P. N.; Niswender, C. M.; Weaver, D. C.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1350. b) Dow, R. L.; Carpino, P. A.; Hadcock, J. R.; Black, S. C.; Iredale, P. A.; DaSilva-Jardine, P.; Schneider, S. R.; Paight, E. S.; Griffith, D. A.; Scott, D. O.; O'Connor, R. E.; Chudy, I. ; Nduaka, C. I. *J. Med. Chem.* **2009**, *52*, 2652.

9. Yu, T. R.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782-2783. (b) Yu, T. R.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370-12371. (c) Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231-1234. (d) Ozawa, T.; Horie, H.; Kurahashi, T.; Matsubara, S. *Chem. Commun.*, **2010**, *46*, 8055-8057.

10. Cobalt catalyzed pyridine synthesis: a) Bonnemann, H.; Brinkman, R.; Schenklum, H. *Synthesis* **1974**, *8*, 575. b) Brien, J. D.; Naiman, A.; Vollhardt, P. K. C. *J. Chem. Soc. Chem. Commun.* **1982**, 133-134. c) Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131.

11. Rhodium pyridine catalysts: a) Cioni, P.; Diversi, P.; Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Mol. Catal.* **1987**, *40*, 337-357. b) Cioni, P.; Diversi, P.;Ingrosso, G.; Lucherini, A.; Ronca, P. *J. Organometal. Chem.* **1993**, *447*, 291. c) Tanaka, K.; N. Suzuki, N.; G. Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917. d) Komine, Y.; Tanaka, K. *Org. Lett.* **2010**, *12*, 1312

12. Ru pyridine catalysts: a) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**,*123*, 6189. b) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; K. Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605. c) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, *68*, 8595.

13. Nickel pyridine catalysts: a) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*,5059. b) McCormick, M. M.; Duong, H. A; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030; c) Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J. *J. Org. Chem.* **2006**, *71*, 5834

14. Titanium pyridine catalysts: Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774

15. Tantalum pyridine catalysts: Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett.* **1995**, 851.

16. Iron pyridine synthesis: a) Ramsay, W. *Philos. Mag.* **1876**, *2*, 269. (b) Ramsay, W. *Philos. Mag.* **1877**, *4*, 241. c) Ferré, K.; Toupet, L.; Guerchais, V. *Organometallics* **2002**, *21*, 2578. d) Schmidt, U.; Zenneck, U. *J. Organomet. Chem.* **1992**, *440*, 187. e) Knoch, F.; Kremer, F.; Schmidt, U.; Zenneck, U.; Floch, P. L.; Mathey, F. *Organometallics* **1996**, *15*, 2713.

CHAPTER 2

NICKEL-CATALYZED CYCLOADDITION OF ENYNES AND ISOCYANATES

Introduction

Our group is interested in utilizing the transition metal catalyzed [2+2+2] cycloaddition reactions[1,2] to construct such structurally useful and biologically relevant cores. In 2004, we reported the use of a Ni and IPr (an *N*-heterocyclic carbene ligand) catalyst system for the coupling of diynes and nitriles to prepare pyridine rings[3] in high yields at room temperature (Equation 2.1). The potential of the Ni/NHC catalytic system was later extended to synthesis of substituted pyridones[4] which can be accessed by the coupling of diynes and isocyanates (Equation 2.2). A year later, our group demonstrated that enynes[5] and aldehydes couple under Ni/NHC conditions to afford a mixture of enones and ketones with excellent regioselectivity for the enone product (>95:5) (Equation 2.3).

The lactam core is prevalent in various natural products and biologically relevant compounds.[6] We envisioned that lactams could be constructed by the cycloaddition of enynes and isocyanates under Ni catalyzed conditions (Equation 2.4). The cycloaddition

of enynes and isocyanates had previously not been studied. This prompted us to investigate this reaction. Currently, only two examples are reported in literature for the cycloaddition of an alkene, alkyne, and isocyanates. The first one is the cycloaddition utilizing an alkenyl-isocyanate (Equation 2.5) and an alkyne using a rhodium[7a] catalyst to obtain a vinylogous amide and a lactam product. A high selectivity of >20:1 was observed favoring the vinylogous amide product. This methodology was also extended to access structural cores of lasubine alkaloids. Matsubara[7b] has demonstrated a Ni/IPr catalyzed cycloaddition of alkynes, acrylates, and isocyanates affording two regioisomers of γ-butyrolactams with moderate regioselectivity and yields (Equation 2.6).

In order to predict the reactivity of enynes with isocyanates, we need to first know whether enynes and isocyanates react under cycloaddition reaction conditions. Earlier reports indicate that enynes are reactive substrates under Ni/NHC catalytic conditions. They readily undergo cycloisomerization[8a] to form conjugated dienes (Equation 2.7). A previous report has shown that isocyanates can undergo trimerization[8b] in the presence of catalytic NHCs to isocyanurates (Equation 2.8). With these two competing side reactions it was unclear if the reaction of enynes and isocyanates would cyclize in a productive manner. However, we were encouraged by a report by Jamison[9] demonstrating that 1,1- and 1,2-disubstituted acrylamides (Equation 2.9) can be prepared by reacting alkenes and alkyl isocyanates with a Ni/IPr catalyst system. This was the first example of an oxidative coupling of an alkene and an isocyanate using a Ni/NHC catalyst system. This suggested that enynes and isocyanates together in a cycloaddition reaction could be reactive under nickel catalyzed conditions.

Results and Discussion

Our initial efforts where to develop optimum reaction conditions that would yield the desired lactam product in good to excellent yields. As shown in Table 2.1, a variety of phosphines and NHCs were evaluated as prospective ligands to determine the potential reactivity between enyne **1a** and cyclohexyl isocyanate **2a** (Table 2.1, Equation 2.10). No enyne and isocyanate coupling product was observed when $Ni(COD)_2$ was used in the absence of a donor ligand (Table 2.1, entry 1). Low conversions of enyne **1a** were observed with monodendate phosphines (entries 2-4) with no detectable product by gas chromatography. Poor conversions and no detectable product was also observed when bidentate phosphines were employed (Table 2.1, entries 5-7). A slight increase in the conversion of starting material was observed when the reaction was run with bulky NHCs such as I^{t}Bu and IMes (Table 2.1, entries 8-9). However, in all cases (Table 2.1, entries 2-9), no detectable coupling product was observed. In contrast, when bulkier NHC ligands such as SIPr and IPr were employed, a distinct coupling product were isolated in good yields (Table 2.1, entries 10-11). Isolation of the major product revealed that cyclization did indeed occur. Dienamides **3a**, rather than a lactam product were isolated in 70 % yield. Interestingly the two dienamide products isolated were namely *E*- and Z- products. The structures of these products were unambigiously assigned by ^{1}H and ^{13}C NMR, and finally by nOe (Nuclear Overhauser effect) correlations.

We propose the following mechanisms for the formation of the dienamide products as shown in Scheme 2.1. In mechanism A (Scheme 2.1, Equation 2.11), initial oxidiative coupling and subsequent insertion leads to 7-membered intermediate **5**. Rather than undergoing C-N bond-forming reductive elimination,[10] β-hydride elimination occurs

resulting in nickelacycle **6**. Facile reductive elimination from nickelacycle **6** would afford the *Z*-dienamide product **3**. Alternatively, mechanism B (Scheme 2.2, Equation 2.12) could involve the oxidative coupling between the isocyanate and the alkyne of the enyne followed by the insertion of the pendant olefin to afford nickelacycle **5** which may undergo β-hydride elimination. Again, facile reductive elimination from nickelacycle would afford the *Z*-dienamide.

The proposed mechanism explains only the formation of the *Z*-dienamide product. In order to better understand the *E*- and *Z*-dienamide product formation, we subjected the *E* and *Z* isomers of dienamide **3b** to the reaction conditions. Thus when the *E*-isomer of **3b** was resubjected to the reaction conditions, no isomerization to the *Z*-dienamide was observed (Scheme 2.1, Equation 2.13). However, when the *Z*-isomer of **3b** was resubjected to the reaction conditions, a mixture of *E*- and *Z*- products were obtained (Scheme 2.1, Equation 2.14). Also, no isomerization was observed when the *E*- and the *Z*- isomers were resubjected to the IPr ligand in the absence of nickel catalyst. Thus, the *Z*-dienamide could most likely be the initial coupling product and undergo a Ni(0)-mediated interconversion to the more stable *E*-isomer over the course of the reaction.

The combination of Ni and IPr catalyzed the coupling of enyne **1a** with a variety of isocyanates (Table 2.2). Alkyl isocyanates reacted smoothly at room temperature within 1-2 h. Furthermore, these reactions afforded dienamides in excellent overall yields with good *E*:*Z* ratios (Table 2.2, entries 1-3). In contrast, aryl isocyanates reacted more sluggishly and required slightly more forcing conditions.[9] For example, the Ni-catalyzed coupling of enyne **1a** and phenyl isocyanate **2d** proceeded at 60 °C while no reaction occurred at room temperature (entry 4). Nevertheless, dienamide **3d** was isolated in 89

% yield. Both aryl isocyanates possessing electron-donating groups as well as electron-withdrawing groups were converted to their respective dienamides in 71 % and 80 % yield (Table 2.2, entries 5 and 6 respectively). Aryl isocyanates possessing electron-withdrawing groups reacted slower than those possessing electron-donating groups (Table 2.2, entries 5-7). Sterically-hindered aryl isocyanates such as **2h** and **2i** were also converted to their respective dieneamides, although under higher reaction temperatures, in good yields, 71 % and 80 %, respectively (Table 2.2, entries 8-9). No desired dienamide product was observed when TMS-NCO was employed. Only the cycloisomerization of enyne **1a** was observed.

A variety of enynes were successfully converted to their respective dienamide products (Table 2.3). A significant increase in dienamide yield (**3j** and **3k**) was observed when ethyl-substituted enyne **1b** was used as a coupling partner in lieu of methyl-substituted enyne **1a** despite the similarity in the backbones of these two substrates (Table 2.3, entries 1-2 versus Table 1.2, entries 1 and 4, respectively). A five carbon linker enyne **1c** afforded a five membered cyclic dienamide in good yield (Table 2.3, entries 3-4). Dienamides having a bicyclic ring system with a nitrogen atom on the bridgehead were also prepared in good yields (Table 2.3, entries 5-6). Although enyne which possesses a bulky trimethylsilyl group on the alkyne, has been used as a substrate in other Ni-catalyzed cycloddition reactions,[5b] this enyne undergoes cycloisomerization[8a] exclusively and does not afford a dienamide product.

Enynes with internal alkynes afforded good to excellent yields for the dienamide products. We turned our attention to enynes with terminal alkynes. Interestingly, when terminal enyne **1f** was subjected to the coupling conditions with either

cyclohexylisocyanate **2a** or phenyl isocyanate **2d**, dienamide formation did not occur. Instead, lactam **10** or **11** was formed as the sole product, albeit in low yields (Equation 2.15).

Lactams **10** and **11** likely arise from C-N bond-forming reductive elimination from a seven membered nickelacycle such as 7**b** (Scheme 2.3). Insertion of the isocyanate into the Ni-sp^3 bond rather than the Ni-sp^2 bond in nickelacycle **4**, would lead to the formation of **5b** (Scheme 2.3, Pathway **B**). Alternatively, nickelacycle **5b** may arise from the initial oxidative coupling between the enyne and the isocyanate followed by insertion of the pendant alkyne (Scheme 2.3, Pathway B). Formation of nickelacycle **5b** may be favored over **5a** when the steric interaction of the alkyne substitutent and the ligand (i.e. IPr) is small. In fact, we have observed this type of sterically-driven selectivity in other Ni-catalyzed[8] cycloaddition chemistry.

Iminoethers are useful building blocks which could be hydrolyzed furthur under mild reaction conditions. Dienamides can be conveniently converted to iminoethers.[11] For example, the reaction of **3b** with *N*-bromosuccinimide (NBS) afforded the bromosubstituted iminoether **12** in 53 % isolated yield (Equation 2.16). Furthermore, when **3b** was subjected to I_2 in lieu of NBS, higher yields were obtained of the halo substituted iminoether. That is, the iodo-substituted iminoether **13** was obtained in 90 % isolated yield (Equation 2.16).

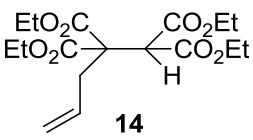
Conclusions

Enynes can be prepared from readily available starting materials and undergoes the cycloaddition reaction with isocyanates using $Ni(COD)_2$ and IPr ligand system to afford dienamides in good to excellent yields. Both alkyl and aryl isocyanates undergo coupling with enynes. In previous Ni-catalyzed reactions arylisocyanates reacted very sluggishly in low yields. However, under Ni/IPr catalytic conditions arylisocyantes react very smoothly affording dienamides in good yields. This catalyst system can be used to prepare dienamides containing five- or six- membered rings. In our substrate scope we have tested enynes with terminal alkenes.

Experimental

All reactions were carried out in the dry glove box until otherwise specified. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem Chemicals and used without further purification. Sodium hydride used was previously washed with hexanes, dried under reduced pressure prior to use. Enyne **1a-1g were** prepared analogously to known literature procedures.[5a] IPr, SIPr, IMes, and I^{t}Bu ligands were prepared as previously reported.[12] The compounds 1-bromo-2-methylbutyne was prepared from the corresponding alcohol.[13] Allyl bromide, 3-bromoprop-1-yne, (3-bromoprop-1-ynyl)trimethylsilane, tetraethyl-1,1,2,2-ethanete tracarboxylate, and isocyanates **2a**-**2j** were purchased from Sigma Aldrich Chemicals.

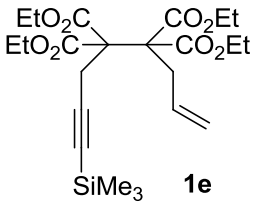
All isocyanates were dried over calcium hydride and distilled under freeze-pump-thaw technique. ^{1}H, ^{13}C, nOe, and HMBC nuclear magnetic resonance spectra of pure compounds were acquired at 300, 400, and 500 MHz instruments. All spectras were carried out using $CDCl_3$ and C_6D_6 as the solvent purchased from Cambridge Isotope Labs. Inc. All spectra are referenced to a singlet of chloroform at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.26 ppm for ^{13}C or 7.16 ppm for ^{1}H and 126.80 ppm for ^{13}C unless specified otherwise. The abbreviations s, d, dd, t, q, quint, sept, and m stand for singlet, doublet, doublet of doublets, triplet, quartet, quintet, septet, and multiplet in that order. All ^{13}C NMR spectra were proton decoupled. (*E*-), (*Z*-) geometry of the dienamides was confirmed by nOe experiments (nuclear Overhauser effect). IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using a NaCl crystal. Gas chromatography were performed on an Agilent 6890 instrument with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 25 °C/min.; final temperature: 300 ºC held for 7 min; detector temperature: 250 ºC.



14

Preparation of tetraethylpent-4-ene-1,1,2,2-tetracarboxylate (**14**): To a stirring suspension of NaH (415 mg, 17.3 mmol) in 150 ml THF (Equation 2.17) was added tetraethyl-1,1,2,2-ethanetetracarboxylate (5.0 g, 15.7 mmol) under N_2 counter-flow in two portions (Equation 2.17). The resulting solution was stirred at room temperature for 1 h after which time allyl bromide (2.1 g, 17.3 mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux for 8 h at which time GC analysis showed no starting ester remained. The solution was cooled to room temperature and quenched with 100 ml of a saturated NH_4Cl

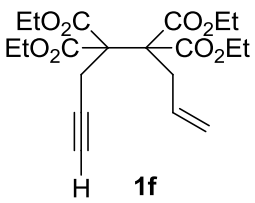
solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organics were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude yellow oil was purified by flash column chromatography (10 % EtOAc/hexanes then 12 % EtOAc/hexanes) to yield **14** (5.3 g, 94 %) as a pale yellow oil. Spectral data were compared with literature values[1].



1e

Preparation of tetraethyl 8-(trimethylsilyl)oct-1-en-7-yne-4,4,5,5-tetracarboxylate (**1e**): To a stirring solution of NaH (147 mg, 6.14 mmol) in 20 ml THF, tetraethyl-pent-4-ene-1,1,2,2-tetracarboxylate (**14**) in 8 ml THF was added. The resulting mixture was stirred at room temperature for 1 h. To this reaction mixture was added (3-bromoprop-1-ynyl)trimethylsilane (1.17 g, 6.14 mmol) in a single portion (Equation 2.18). The resulting solution was refluxed for 48 h. After checking the completion of the reaction by gas chromatography, the reaction mixture was quenched by the addition of saturated NH_4Cl (10 ml) and H_2O (10 ml). To the reaction mixture Et_2O (20 ml) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 ml). All organic layers were combined and washed with brine (10 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with 10 % EtOAc/hexanes to yield enyne **1e** as a yellow oil (862 mg, 66 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.82-6.13 (m, 1H), 5.05-5.12 (m, 2H), 4.15- 4.32 (m, 8H), 3.20 (s, 2H), 2.80 (d, J = 6.9 Hz, 2H), 1.25-1.30 (m, 12H), 0.20 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.3, 168.8, 134.0, 119.1, 102.9, 87.1, 62.6, 62.3, 62.1, 61.8, 36.5, 23.7, 14.0, 14.1, 0.1. IR (neat): 3080, 2983,

2906, 2182, 1737, 1639, 1445, 1390, 1367, 1207, 1033, 920, 847 cm-^{1}. **HRMS** calculated *m/z* for $C_{23}H_{36}O_8NaSi$ (M^+Na) 491.2077, found 491.2071.

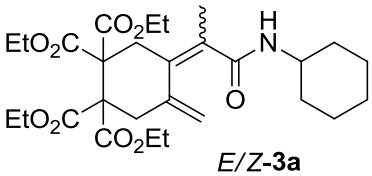


1f

Preparation of tetraethyl-oct-1-en-7-yne-4,4,5,5-tetracarboxylate (**1f**): To a stirring solution of NaH (294 mg, 12.3 mmol) in 50 ml THF was added compound **14** (2.0 gms, 5.58 mmol). The reaction mixture was stirred for 1 h after which 3-bromoprop-1-yne (1.46 g, 12.3 mmol) as an 80% w/v solution in toluene in a single portion (Equation 2.19). The reaction mixture was stirred for 1 h and then the resulting mixture was refluxed for 24 h. After checking the completion of the reaction by gas chromatography, the reaction mixture was quenched by the addition of saturated NH_4Cl (20 ml) and H_2O (20 ml). To the reaction mixture Et_2O (20 ml) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 20 ml). All organic layers were combined and washed with brine (20 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with 30 % ethyl acetate/hexanes to yield enyne **1f** as a colorless solid (1.79 g, 81 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.81-6.11 (m, 1H), 5.05-5.20 (m, 2H), 4.15-4.30 (m, 8H), 3.15 (d, J = 2.4 Hz, 2H), 2.81 (d, J = 7.2 Hz, 2H), 2.07 (t, J = 2.7 Hz, 1H), 1.20-1.40 (m, 12H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.1, 168.8, 133.8, 119.4, 80.2, 70.8, 62.1, 62.0, 61.9, 36.4, 22.4, 14.0. IR (neat): 3277, 3080, 2984, 2906, 1736, 1639, 1445, 1390, 1367, 1209, 1035, 864 cm^{-1}. **HRMS** calculated *m/z* for $C_{20}H_{28}O_8Na$ (M^+Na) 419.1682, found 419.1684.

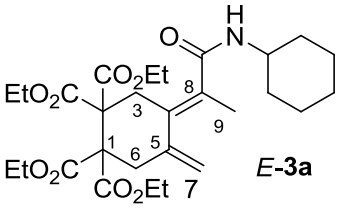
General Cycloaddition Procedure

In a dry glove box, the enyne and isocyanate was added to an oven dried scintillation vial equipped with a magnetic stir bar and dissolved in toluene. To this reaction mixture, a solution of $Ni(COD)_2$ and IPr which was previously equilibrated for atleast 4 h was added using a calibrated microsyringe. The reaction mixture was stirred at room temperature or heated in an oil-bath at the desired temperature until the reaction was complete. The consumption of starting material was monitored by GC. The mixture was concentrated under reduced pressure and purified by silica gel column chromatography.



E/Z-**3a**

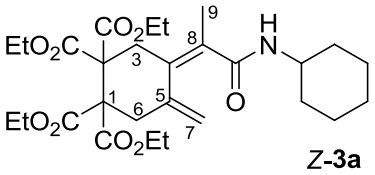
Compounds (*Z*) and (*E*)-tetraethyl-4-(1-(cycloamino)-1-oxopropan-2-ylidene)-5-methylenecyclohexane-1,1,2,2-tetracarboxylate (*Z*/*E*-**3a**): General cycloaddition procedure was used with enyne **1a** (100 mg, 0.24 mmol), cyclohexyl isocyanate (30.5 mg, 0.24 mmol) **2a**, $Ni(COD)_2$ (6.77 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 1 h at room temperature. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compounds ***E*-3a** as a colorless solid (m.p. 130-132 °C) and ***Z*-3a** as an oil (90.3 mg, 70 %).



***E*-3a**

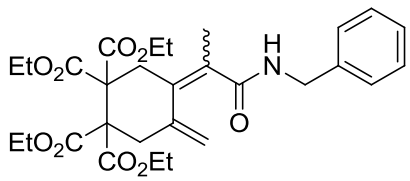
***E*-3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.82 (d, J= 8.8 Hz, 1H), 5.35 (s, 1H), 4.90 (s, 1H), 4.2 (m, 8H), 3.80-3.85 (m, 1H), 3.05 (d, J = 6 Hz, 4H), 1.98 (s, 3H), 1.9-1.1 (brm, 10H), 1.2-1.3 (q, J = 5.2 Hz, 12H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.8, 169.7, 169.2, 139.7, 131.6, 130.5, 116.8, 61.9, 61.8, 60.7, 58.8, 47.8, 39.7, 35.4, 33.2, 25.7, 24.9, 17.7, 14.1, 13.9. IR (neat): 3608, 3583, 2983, 2933, 2260, 1740, 1262, 1207 cm^{-1}. nOe correlation was seen with a proton on C-7 and

the methyl protons on C-9. HRMS calculated *m/z* for $C_{28}H_{41}NO_9Na$ (M^+Na) 558.2679, found 558.2670.



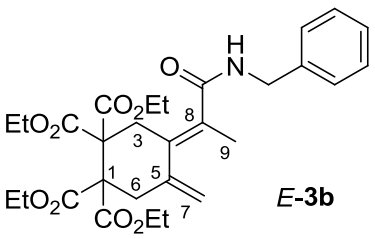
Z-**3a**

***Z*-3a:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.6 (m, 2H), 4.1-4.2 (m, 8H), 3.6-3.8 (s, 1H), 3.20 (s, 2H), 2.90 (s, 2H), 1.90 (s, 3H), 1.5-1.75 (m, 6H), 1.05-1.20 (m, 16H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 169.5, 169.4, 141.0, 133.6, 131.5, 116.6, 62.1, 61.9, 60.9, 58.8, 47.7, 39.0, 33.4, 32.5, 30.5, 29.9, 25.8, 24.9, 16.0, 14.1, 14.0. IR (neat): 3583, 3392, 2984, 2933, 2855, 2253, 1730, 1656, 1267, 912 cm^{-1}. nOe correlation was seen with vinylic proton on C-7 and methylene protons on C-6. HRMS calculated *m/z* for $C_{28}H_{41}NO_9Na$ (M^+Na) 558.2679, found 558.2673.



E/Z-**3b**

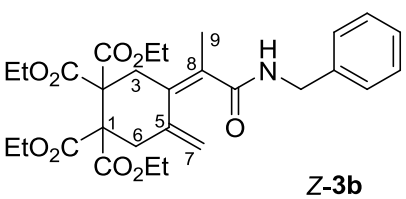
<u>Compounds (*Z*) and (*E*)-tetraethyl 4-(1-(benzylamino) 1-oxopropan-2-ylidene)-5-methylenecyclohexane-1, 1, 2,2-tetracarboxylate (***E*/*Z*-3b**): </u>General procedure was used with enyne **1a** (100 mg, 0.24 mmol), benzyl isocyanate (32.4 mg, 0.24 mmol) **2b**, $Ni(COD)_2$ (6.77 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 2 h at room temperature. The crude compound was purified by flash chromatography eluting with 30 % EtOAc to yield compound ***E*-3b** as a colorless solid (m.p. 95-98 °C) and compound ***Z*-3b** as an oil (90 mg, 68 %).



E-**3b**

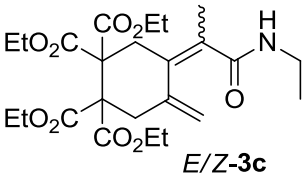
***E*-3b:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)7.20-7.40 (m, 5H), 5.92 (t, *J* = 6.3 Hz, 1H), 5.0 (s, 1H), 4.71 (d, *J* = 1.2 Hz, 1H), 4.34 (d, *J* = 5.7 Hz, 2H), 4.25-4.13 (m, 8H), 3.05

(s, 2H), 2.84 (s, 2H), 1.94 (s, 3H), 1.15-1.25 (m, 12H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 172.4, 169.4, 169.3, 140.9, 138.2, 134.2, 130.8, 128.7, 128.1, 127.5, 116.6, 62.1, 61.9, 60.8, 58.7, 43.9, 38.9, 33.5, 16.1, 14.1, 14.0. IR (neat): 3396, 2983, 1735, 1659, 1266, 1204, 864 cm^{-1}. nOe correlation was seen with a proton on C-7 and the protons on C-9. HRMS calculated for *m/z* $C_{29}H_{37}NO_9Na$ (M^+Na) 566.2366, found 566.2360.



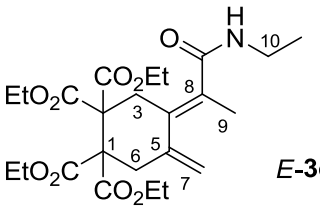
Z-**3b**

***Z*-3b:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.29-7.25 (m, 5H), 6.26 (t, *J* = 5.4 Hz, 1H), 5.12 (m, H), 4.94 (d, *J* = 1.8 Hz, 1H), 4.54 (d, *J* = 6.3 Hz, 2H), 3.8 - 4.2 (m, 8H), 2.98 (d, *J* = 15.9 Hz, 4H), 1.98 (s, 3H), 1.25 -1.05 (m, 12 H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 171.6, 169.7, 169.2, 139.8, 138.4, 132.3, 129.6, 128.8, 128.1, 127.6, 116.9, 61.9, 61.9, 60.8, 58.8, 43.6, 39.6, 35.7, 14.0, 13.8. IR (neat): 3396, 2983, 1735, 1659, 1266, 1204, 1041, 912 cm^{-1}. nOe correlation was seen with vinylic proton on C-7 and methylene protons on C-6. HRMS calculated for *m/z* $C_{29}H_{37}NO_9Na$ (M^+Na) 566.2366, found 566.2369.



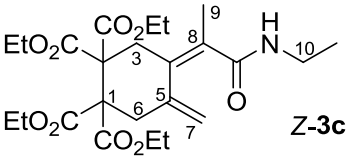
E/Z-**3c**

<u>Compounds (*Z*) and (*E*)-tetraethyl 4-(1-(ethylamino)-1-oxo propan-2-ylidene)-5-methylenecyclohexane-1,1,2,2-tetracarb-oxylate (***Z*/*E*-3c**)</u>: General cycloaddition procedure was used with enyne **1a** (100 mg, 0.24 mmol), ethyl isocyanate (17.3 mg, 0.24 mmol) **2c**, $Ni(COD)_2$ (6.77 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 2 h at 80 °C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E*-3c** as a colorless solid (m.p. 98-100 °C) and compound ***Z*-3c** as an oil (94 mg, 80 %).



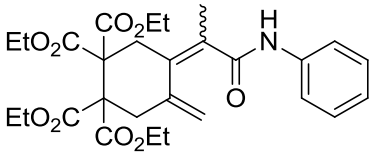
E-**3c**

***E*-3c:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.59 (brs, 1H), 5.10 (s, 1H), 4.90 (s, 1H), 4.18-4.28 (m, 8H), 3.21 (q, J = 6.4 Hz, 2H), 2.89 (s, 4H), 1.60 (d, J = 6.4 Hz, 3H), 1.15-1.25 (m, 12H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 171.7, 169.8, 169.3, 139.6, 131.8, 130.4, 117.0, 62.0, 60.7, 58.9, 39.6, 35.5, 34.2, 17.8, 14.9, 14.1, 13.9. IR (neat): 3609, 3584, 2982, 1738, 1647, 1367, 1263, 1209, 1042, 864 cm^{-1}. nOe correlation was seen with a proton on C-7 and the methyl protons on C-9. HRMS *m/z* calculated for $C_{24}H_{35}NO_9Na$ (M^+Na) 504.2210, found 504.2209.



Z-**3c**

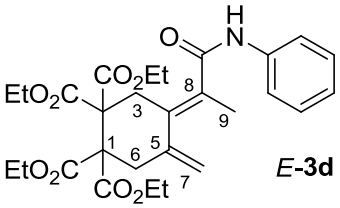
***Z*-3c:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.59 (*t*, J = 5.6 Hz, 2H), 5.10 (s, 1H), 4.90 (s, 1H), 4.15 -4.24 (m, 8H), 3.21 (q, J= 6.6 Hz, 2H) 3.14 (s, 2H), 2.84 (s, 2H), 1.84 (s, 3H), 1.26 (m, 12H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 172.5, 169.5, 169.4, 141.0. 133.8, 131.2, 116.4, 61.8, 61.7, 58.5, 55.9, 31.4, 14.0, 12.9, 3.8. IR (neat): 3584, 3402, 2982, 1735, 1519, 1266, 913 cm^{-1}. nOe correlation was seen with vinylic proton on C-7 and methylene protons on C-6. HRMS *m/z* calculated for $C_{28}H_{41}NO_9Na$ (M^+Na) 504.2210, found 504.2207.



E/*Z*-**3d**

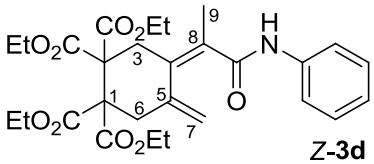
<u>Compounds (*Z*)- and (*E*)-tetraethyl- 4-methylene-5-(1-oxo1-(phenylamino)propan-2-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (***Z*/*E*-3d**):</u> General cycloaddition procedure was used with enyne **1a** (100 mg, 0.24 mmol), phenyl isocyanate (29.1 mg, 0.24 mmol) **2d**, $Ni(COD)_2$ (6.77 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 2 h at 60 °C. The crude compound was

purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E*-3d** and compound ***Z*-3d** as oils (105 mg, 79 %).



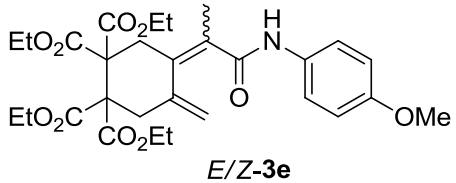
E-3d

***E*-3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm). 8.10 (s, 1H), 7.5 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 6Hz, 2H), 7.13 (t, J = 5.4 Hz, 1H), 5.20 (s, 1H), 4.99 (s, 1H), 4.15-4.26 (m, 8H), 3.16 (s, 2H), 2.99 (m, 2H), 2.07 (s, 3H), 1.15-1.4 (m, 12H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.2, 139.5, 138.3, 132.2, 130.5, 129.2, 124.3, 119.8, 117.3, 62.2, 62.1, 60.4, 59.3, 39.8, 35.6, 18.1, 14.1, 13.9. IR (neat): 3348, 2984, 1738, 1673, 1532, 1441, 1266, 1041, 915, 732 cm^{-1}. nOe correlation was seen with a proton on C-7 and the methyl protons on C-9. HRMS calculated *m/z* for $C_{28}H_{35}NO_9Na$ (M^+Na) 552.2210, found 552.2205.



Z-3d

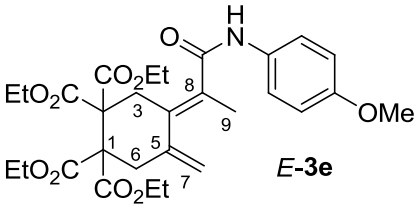
***Z*-3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 (s, 1H), 7.48 (d, J = 8 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.09 (t, J = 4.1 Hz, 1H), 5.20 (s, 1H), 4.99 (s, 1H), 4.25 (m, 8H), 3.23 (s, 2H), 2.89 (s, 2H), 1.95 (s, 3H), 1.42-1.28 (m, 12H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.6, 169.5, 169.4, 141.2, 138.7, 135.3, 131.4, 129.1, 124.2, 119.8, 117.1, 62.2, 62.1, 60.9, 58.6, 38.7, 33.5, 15.9, 14.1, 14.0. IR (neat): 3365, 2984, 1739, 1681, 1598, 1440, 1267, 1043, 915 cm^{-1}. nOe correlation was seen with vinylic proton on C-7 and methylene protons on C-6. HRMS calculated for *m/z* $C_{28}H_{35}NO_9Na$ (M^+Na) 552.2210, found 558.2208.



E/*Z*-3e

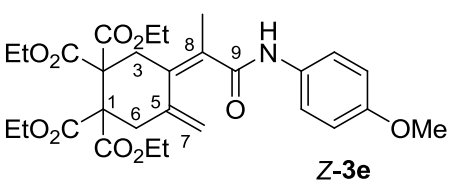
<u>Compounds (*Z*) and (*E*)-tetraethyl 4-(1-(4-methoxyphenylamino)-1-oxopropan-2-ylidene)-5-methyl-</u>

enecyclohexane-1,1,2,2-tetracarboxylate (***Z*/*E*-3e**): General cycloaddition procedure was used with enyne **1a** (100 mg, 0.24 mmol), *p*-methoxyphenyl isocyanate (36.3 mg, 0.24 mmol) **2e**, $Ni(COD)_2$ (6.7 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 2 h at 60° C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E*-3e** as a colorless solid (m.p. 119-120 °C) and compound ***Z*-3e** as an oil (102 mg, 74 %).



E-3e

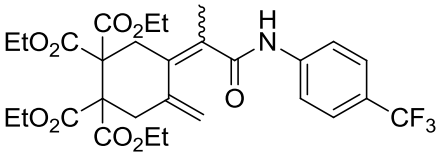
***E*-3e:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (s, 1H), 7.48 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.19 (s, 1H), 5.0 (s, 1H), 4.05 -4.20 (m, 8H), 3.80 (s, 3H), 3.15 (s, 2H), 2.99 (s, 2H), 2.07(s, 3H), 1.05-1.25 (m, 12H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.7, 169.2, 156.6, 139.7, 132.3, 131.4, 130.6, 121.7, 117.2, 114.4, 62.2, 62.0, 60.5, 59.4, 55.7, 39.9, 35.7, 18.0, 14.1, 13.9. IR (neat): 3351, 2984, 2253, 1739, 1513, 1248, 1038 cm^{-1}. nOe correlation was seen with a proton on C-7 and the methyl protons on C-8. HRMS calculated for *m/z* $C_{29}H_{37}NO_{10}Na$ (M^+Na) 582.2315, found 582.2314.



Z-3e

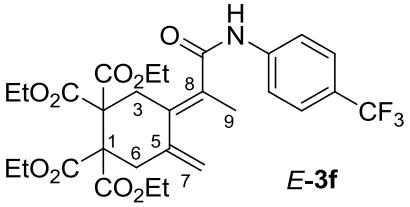
***Z*-3e:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (s, 1H), 7.38 (d, J = 9.2 Hz, 2H), 6.85 (d, J = 9.2 Hz, 2H), 5.16 (s, 1H), 4.94 (s, 1H), 4.05-4.24 (m, 8H), 3.79 (s, 3H), 3.23 (s, 2H), 2.88 (s, 2H), 1.94 (s, 3H), 1.20-1.28 (m, 12H) . ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.5, 169.5, 169.4, 156.7, 141.3, 135.1, 131.9, 131.5, 121.7, 116.9, 114.4, 62.2, 62.1, 61.1, 58.7, 55.7, 38.8, 33.6, 29.9, 16.0, 14.1, 14.0. IR (neat): 3372, 2985, 2937, 2253, 1729, 1513, 1268, 911 cm^{-1}. nOe correlation was seen

with vinylic proton on C-7 and methylene protons on C-6. HRMS calculated for *m/z* $C_{29}H_{37}NO_{10}Na$ (M^+Na) 582.2315, found 582.2313.



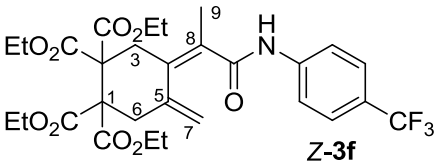
E/Z-**3f**

Compounds (*Z*) and (*E*)-tetraethyl- 4-methylene-5-(1-oxo-1-(4-(trifluoromethyl)phenylamino)propan-2-ylidene)cyclohexane-1,1,2,2-tetracarboxylate (***Z/E*-3f**): General cycloaddition procedure was used with enyne **1a** (100 mg, 0.24 mmol), 4-trifluoromethylphenyl isocyanate (36.3 mg, 0.24 mmol) **2f**, $Ni(COD)_2$ (6.8 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 7 h at 100° C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E*-3f** and compound ***Z*-3f** as oils (83.2 mg, 57 %).



***E*-3f**

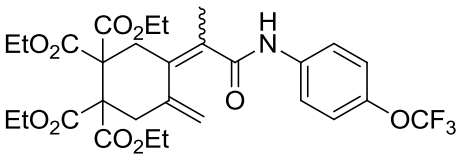
***E*-3f:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.52 (s, 1H), 7.72 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 5.22 (s, 1H), 5.01 (s, 1H), 4.15-4.21 (m, 8H), 3.16 (s, 2H), 2.95 (s, 2H), 2.08 (s, 3H), 1.15-1.40 (m, 12H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.2, 169.9, 169.1, 141.5, 139.4, 132.8, 130.2, 126.5 (q, J= 18.4 Hz), 119.4, 117.6, 62.4, 62.1, 60.3, 59.6, 39.9, 35.7, 18.1, 14.1, 13.9. IR (neat): 3339, 2985, 2940, 2257, 1737, 1684, 1368, 1262 cm^{-1}. HRMS calculated for *m/z* $C_{28}H_{41}NO_9Na$ (M^+Na) 620.2083, found 620.2079.



Z-**3f**

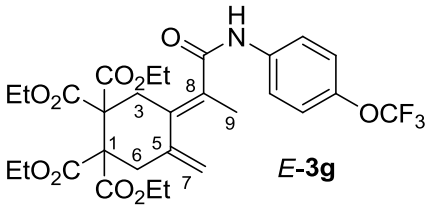
***Z*-3f:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm). 7.79 (s, 1H), 7.59 (m, 4H), 5.14 (s, 1H), 4.93 (s, 1H), 4.15-4.25 (m, 8H), 3.24 (s, 2H), 2.88 (s, 2H), 1.94 (s, 3H), 1.29 (m, 12H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.9, 169.5, 169.3, 141.9, 141.4, 136.3, 125.7, 126.4 (q, J = 15.2 Hz), 119.4, 119.3, 117.4, 62.3, 62.2, 61.1, 58.6,

38.6, 33.6, 15.9, 14.1, 14.0. IR (neat): 3356, 2986, 1739, 1692, 1324, 1266, 1117, 919 cm^{-1}. nOe correlation was seen with vinylic proton on C-7 and methylene protons on C-6. HRMS calculated for *m/z* $C_{28}H_{41}NO_9Na$ (M^+Na) 620.2083, found 620.2079.



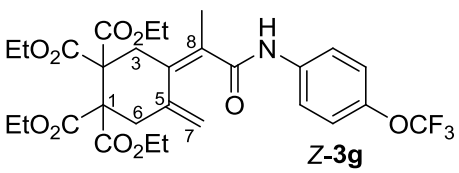
E/Z-**3g**

Preparation of compounds (*Z*)- and (*E*)-tetraethyl-4 methylene-5-(1-oxo-1-(4(trifluoromethoxy)phenyl amino)propan-2-ylidene)cyclohexane-1,1,2,2-tetra carboxylate (***Z***/***E***-**3g**): General cycloaddition procedure was used with enyne **1a** (100 mg, 0.24 mmol), 4-(trifluoromethoxy)phenyl isocyanate (49.5 mg, 0.24 mmol) **2g**, $Ni(COD)_2$ (6.80 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 5 h at 80° C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E***-**3g** and compound ***Z***-**3g** as oils (99.8 mg, 66.7 %).



E-**3g**

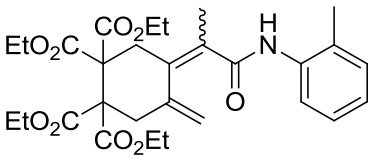
E-**3g:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.36 (s, 1H), 7.61 (d, *J* = 12.4 Hz, 2H), 7.17 (d, *J* = 10.8 Hz, 2H), 5.19 (s, 1H), 4.98 (s, 1H), 4.18 (m, 8H), 3.14 (s, 2H), 2.96 (s, 2H), 2.05 (s, 3H), 1.24 (m, 12H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.1, 145.4, 139.5, 137.1, 132.7, 130.3, 126.49, 121.9, 121.0, 117.4, 62.3, 62.1, 60.3, 59.6, 39.9, 35.7, 18.0, 14.1, 13.9. IR (neat): 3339, 2985, 2874, 1738, 1265, 1203, 1058, 918 cm^{-1}. HRMS calculated for *m/z* $C_{28}H_{41}NO_9Na$ (M^+Na) 636.2033, found 636.2027.



Z-**3g**

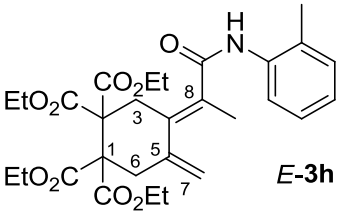
Z-**3g:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67(s, 1H), 7.51 (d, *J* = 9.2 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 5.14 (s, 1H), 4.94 (s, 1H), 4.05-4.25 (m, 8H), 3.24 (s, 2H), 2.88 (s, 2H), 1.93 (s, 3H) 1.05- 1.29 (m, 12H). ^{13}C {^1H} NMR (100 MHz,

$CDCl_3$): δ (ppm) 170.8, 169.5, 169.3, 145.3, 141.4, 137.4, 135.9, 131.2, 121.9, 120.9, 117.2, 62.3, 62.1, 61.1, 58.6, 38.7, 33.5, 15.9, 14.1, 14.0. IR (neat): 3358, 2985, 2940, 2255, 1738, 1682, 1512, 1265, 1200, 1107, 1043, 919, 861 cm^{-1}. nOe correlation was seen between the two vinylic proton on C-7. HRMS calculated for *m/z* $C_{28}H_{41}NO_9Na$ (M^+Na) 636.2033, found 636.2031.

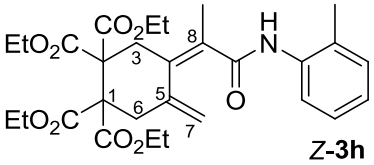


E/*Z*-**3h**

Compounds (*Z*)- and (*E*)-tetraethyl 4-methylene-5-[1-oxo -1-(o-tolylamino) propan-2-ylidene]cyclohexane-1,1,2,2-tetracarboxylate (***Z***/***E***-**3h**): The general cycloaddition procedure was used with enyne **1a** (100 mg, 0.24 mmol), 2-methylphenyl isocyanate (32.4 mg, 0.24 mmol) **2h**, $Ni(COD)_2$ (6.77 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 1 h at 80° C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/ hexanes to yield compounds ***E***-**3h** and ***Z***-**3h** as an inseparable mixture of isomers as an oil (94 mg, 71 %).



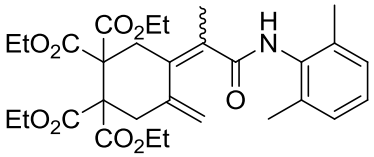
E-**3h**



Z-**3h**

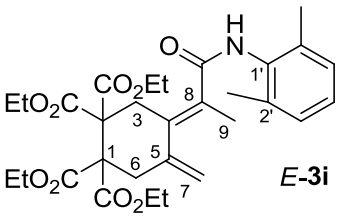
E-**3h** and ***Z***-**3h:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm 7.94 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.60 (s, 1H), 7.44 (s, 2H), 7.23-7.08 (m, 6H), 7.03 (q, *J* = 4.8 Hz, 2H), 5.22-5.19 (m, 3H), 4.99 (d, *J* = 2.1 Hz, 1H), 4.94 (d, *J* = 1.5 Hz, 2H), 4.28 - 4.09 (m, 16H), 3.21 (d, 6H), 3.02 (s, 2H), 2.88 (s, 4H), 2.27 (d, *J* = 11.4 Hz, 8H), 2.10 (s, 3H), 1.95 (s, 6H), 1.31-1.71 (m, 24H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.6, 170.1, 169.7, 169.3, 169.3, 169.2, 141.1, 139.5, 136.4, 135.6, 134.7, 132.4, 131.4, 130.7, 130.5, 130.3, 130.2, 128.2, 126.8, 125.6, 124.6, 123.8, 121.1, 117.3, 62.2, 62.0, 61.9, 60.9, 60.5, 59.0, 58.5,

39.7, 38.9, 35.7, 33.4, 18.1, 17.7, 16.1, 14.0, 13.9, 13.8. IR (neat): 3386, 2983, 2939, 2906, 2248, 1726, 1682, 1517, 1268, 1200, 1096, 1057, 1044, 919, 863, 702 cm^{-1}. HRMS *m/z* calculated for $C_{28}H_{41}NO_9Na$ (M^+Na) 566.2366, found 566.2368.



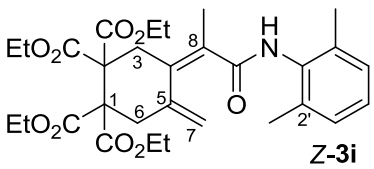
E/Z-**3i**

Compounds (*Z*)- and (*E*)-tetraethyl 4-[1-(2,6)-dimethyl phenylamino]-1-(oxopropan-2-ylidene)-5-methylenecyclo hexane-1,1,2,2-tetracarboxylate (***Z***/***E***-**3i**): General cycload dition procedure was used with enyne **1a** (100 mg, 0.24 mmol), 2,6-dimethylphenyl isocyanate (35.8 mg, 0.24 mmol) **2i**, $Ni(COD)_2$ (6.77 mg, 0.024 mmol), IPr (18.9 mg, 0.048 mmol) and 2.4 ml toluene and stirred for 1.5 h at 80 ° C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E***-**3i** as a colorless solid (m.p. 138-140 °C) and compound ***Z***-**3i** as oil (109 mg, 80 %).



***E*-3i**

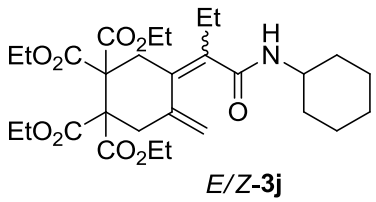
***E*-3i:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 (s, 1H), 7.09 (s, 3H), 5.20 (s, 1H), 4.99 (d, J = 1.2 Hz, 1H), 4.18-4.25 (m, 8H), 3.28 (s, 2H), 3.06 (s, 2H), 2.28 (s, 6H), 2.14 (s, 3H), 1.20-1.24 (m, 12H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.4, 169.8, 169.3, 139.6, 135.8, 133.7, 132.2, 130.1, 128.5, 127.5, 117.2, 62.1, 60.8, 59.1, 39.8, 36.1, 19.0, 18.3, 14.1, 13.9. IR (neat): 3354, 2983, 2240, 1739, 1270, 1041 cm^{-1}. HRMS calculated for *m/z* $C_{30}H_{39}NO_9Na$ (M^+Na) 580.2523, found 580.2515.



***Z*-3i**

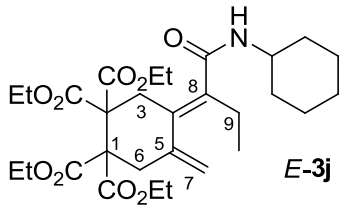
***Z*-3i:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22 (s, 1H), 7.06 (s, 3H), 5.32 (s, 1H), 5.029 (s, 1H), 4.15- 4.23 (m, 8H), 3.29 (s, 2H), 2.90 (s, 2H), 2.23 (s, 6H), 1.98 (s, 3H), 1.15-1.30 (m, 12H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.8, 169.5, 169.4, 141.5, 135.8, 133.9, 133.6, 130.9, 128.6, 127.6, 117.9, 62.24, 62.0, 61.2, 58.7, 39.0, 33.6,

18.7, 16.5, 14.1, 14.0. IR (neat): 3368, 2982, 2360, 1738, 1266, 1041 cm^{-1}. nOe correlation was seen between the two vinylic protons on C-7. HRMS *m/z* calculated for $C_{28}H_{41}NO_9Na$ (M^+Na) 580.2523, found 580.2515.



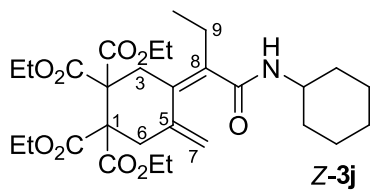
E/Z-**3j**

Compounds (*Z*)- and (*E*)-tetraethyl-4-[1(cyclohexylamino)-1-oxobutan-2-ylidene)-5-methylenecyclohexane-1,1 2,2-tetracarboxylate (***Z/E*-3j**): General cycloaddition procedure was used with enyne **1b** (100 mg, 0.23 mmol), cyclohexylisocyanate (29.5 mg, 0.23 mmol) **2a**, $Ni(COD)_2$ (6.80 mg, 0.023 mmol), IPr (18.9 mg, 0.046 mmol) and 2.3 ml toluene and stirred for 4 h at room temperature. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compounds ***E*-3j** as a colorless solid (m.p. 88- 90 °C) and ***Z*-3j** as an oil (116 mg, 89 %).



***E*-3j**

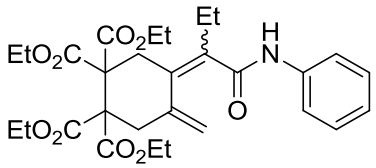
***E*-3j:** ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.81 (d, *J*= 8.7 Hz, 1H), 5.06 (s, 1H), 4.93 (d, *J* = 1.8 Hz, 1H), 4.20 (m, 8H), 3.80-3.91 (m, 1H), 3.0 (d, *J* = 7.2 Hz, 4H), 2.43 (q, *J*= 7.5 Hz, 2H), 1.90-1.95 (m, 2H), 1.6-1.8 (m, 4H), 1.58-1.05 (m, 12H), 0.99 (t, *J*= 7.2, 3H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.8, 169.8, 169.3, 139.9, 136.8, 131.2, 116.1, 62.0, 61.9, 61.0, 58.8, 47.9, 39.8, 35.7, 33.3, 30.5, 29.8, 25.8, 25.0, 24.1, 14.1, 13.9, 13.5. IR (neat): 3385, 3068, 2982, 2253, 1727, 1641, 1268, 1206, 912 cm^{-1}. nOe correlation was seen between a vinylic proton on C-7 and the protons of the ethyl group on C-8. HRMS *m/z* calculated for $C_{29}H_{43}NO_9Na$ (M^+Na) 572.2836, found 572.2831.



***Z*-3j**

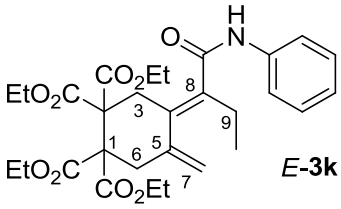
***Z*-3j:** ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.61 (d, *J*= 8.7 Hz, 1H), 5.16 (s, 1H), 4.89 (s, 1H), 4.12- 4.30 (m,

8H), 3.71-3.80 (m, 1H), 3.19 (s, 2H), 2.80 (s, 2H), 2.27 (q, *J*= 5.7 Hz, 2H), 1.7-1.85 (m, 2H), 1.5-1.72 (m, 4H), 1.20-1.0 (m, 16H), 0.94 (t, *J*= 7.5 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 170.9, 169.5, 141.2, 137.8, 133.1, 116.6, 62.2, 61.9, 61.2, 58.6, 47.6, 38.8, 33.1, 32.6, 25.8, 24.9, 23.0, 14.1, 12.8. IR (neat): 3394, 3087, 2981, 2856, 2253, 1730, 1640, 1267, 913 cm^{-1}. nOe correlation was seen between the two vinylic protons on C-7. HRMS *m/z* calculated for $C_{29}H_{43}NO_9Na$ (M^+Na) 572.2836, found 572.2834.



E/Z-**3k**

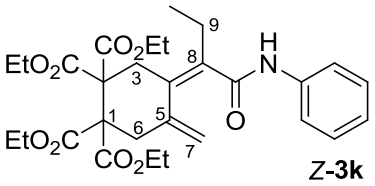
Compounds (*Z*) and (*E*)-tetraethyl 4-methylene-5-(1oxo-1-(phenylamino)butan-2-ylidene)cyclohexane-1,1-2,2-tetracarboxylate (***Z*/*E*-10k**): General cycloaddition procedure was used with enyne **1b** (100 mg, 0.23 mmol), phenylisocyanate (28.1 mg, 0.23 mmol) **2b**, $Ni(COD)_2$ (6.80 mg, 0.023 mmol), IPr (18.9 mg, 0.046 mmol) and 2.3 ml toluene and stirred for 6 h at room temperature. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E*-3k** and compound ***Z*-3k** as oils (115 mg, 89 %).



E-**3k**

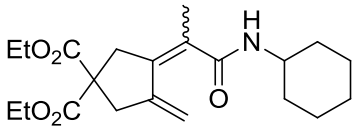
***E*-3k:** ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 5.13 (s, 1H), 5.01 (s, 1H), 4.15-4.24 (m, 8H), 3.13 (s, 2H), 3.02 (s, 2H), 2.54 (q, *J* = 7.6 Hz, 2H), 1.09 (s, 3H), 1.19-1.30 (m, 8H), 1.09 (t, *J* = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.2, 139.9, 138.2, 136.9, 132.0, 129.2, 124.4, 120.0, 116.4, 62.2, 62.1, 60.8, 59.4, 40.0, 36.1, 30.5, 29.9, 24.6, 14.1, 13.9, 13.7. IR (neat): 3370, 2983, 2937, 2253, 1727, 1656, 1270, 1200, 912, 733 cm^{-1}. nOe correlation was seen between a vinylic proton on C-7 and the

protons of the ethyl group on C-8. HRMS *m/z* calculated for $C_{29}H_{37}NO_9Na$ (M^+Na) 566.2366, found 566.2353.



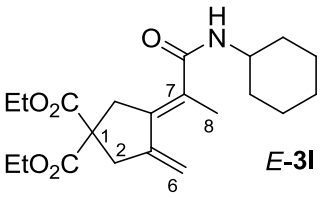
Z-**3k**

***Z*-3k:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.63 (s, 1H), 7.50 (d, J = 5.4 Hz, 2H), 7.31 (t, J = 5.7 Hz, 2H), 7.09 (t, J = 5.4 Hz, 1H), 5.17 (s, 1H), 4.92 (s, 1H), 4.29-4.17 (m, 8H), 3.26 (s, 2H), 2.86 (s, 2H), 2.37 (q, J = 5.7 Hz, 2H), 1.25-1.32 (m, 12H), 1.01 (t, J = 5.7 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 170.3, 169.5, 169.4, 141.5, 138.8, 137.8, 134.9, 129.1, 124.2, 119.8, 117.2, 62.3, 62.1, 61.3, 58.6, 38.6, 33.2, 23.2, 14.1, 12.9. IR (neat): 3372, 2981, 2935, 1727, 1683, 1269, 1039 cm^{-1}. nOe correlation was seen between the two vinylic protons on C-7. HRMS *m/z* calculated for $C_{29}H_{37}NO_9Na$ (M^+Na) 566.2366, found 566.2361.



E/*Z*-**3l**

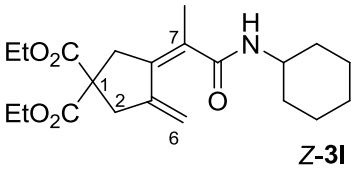
<u>Compounds (*Z*)- and (*E*)-diethyl-3-(1-cyclohexylamino) 1-oxopropan-2-ylidene)-4-methylenecyclopentane-1,1-dicarboxylate (***Z*/*E*-3l**)</u>: General cycloaddition procedure was used with enyne **1c** (50 mg, 0.2 mmol), cyclohexylisocyanate (24.8 mg, 0.2 mmol) **2a**, $Ni(COD)_2$ (5.5 mg, 0.02 mmol), IPr (15.5 mg, 0.04 mmol), 2 ml toluene and stirred for 4 h at 80 °C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compounds ***E*-3l** and ***Z*-3l** as oils (48.7 mg, 65 %).



E-**3l**

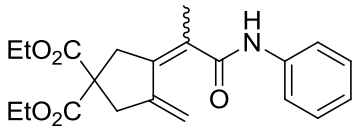
***E*-3l:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.86 (d, J = 8.1 Hz, 1H), 5.25 (d, J = 9.3 Hz, 2H), 4.18 (q, J = 7.2 Hz, 4H), 3.76-3.92 (m, 1H), 3.11 (s, 2H), 3.04 (s, 2H), 2.05 (s, 3H), 1.90-2.02 (m, 2H), 1.56-1.8 (m, 6H), 1.1-1.4 (m, 8H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 171.4, 170.6, 144.7, 135.9, 129.4, 113.7, 61.9, 57.5, 48.3, 42.2, 40.3, 33.2, 30.5,

29.9, 25.7, 25.1, 17.9, 14.2. IR (neat): 3372, 2982, 2933, 2856, 2244, 1730, 1632, 1524, 1242, 971, 733 cm^{-1}. nOe correlation was seen between a vinylic proton on C-6 and the protons of the methyl group on C-8. HRMS *m/z* calculated for $C_{21}H_{31}NO_5Na$ (M^+Na) 400.2100, found 400.2099.



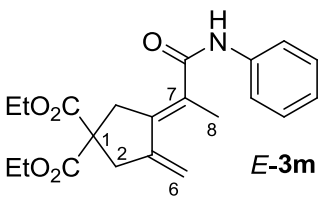
Z-**3l**

***Z*-3l:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.44 (d, J = 8.4 Hz, 1H), 5.32 (s, 1H), 5.06 (s, 1H), 4.19 (q, J = 7.5 Hz, 4H), 3.70-3.88 (brm,1H), 2.97-3.02 (s, 3H), 1.92 (s, 3H), 1.8-1.9 (m, 2H), 1.57-1.77 (m, 6H), 1.32-1.10 (m, 8H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 171.4, 170.7, 142.5, 134.3, 128.5, 111.0, 61.9, 57.0, 48.0, 42.4, 39.0, 32.7, 25.7, 25.0, 19.1, 14.2. IR (neat): 3375, 3285, 2981, 2931, 2855, 2361, 1733, 1625, 1247, 1190, 1159, 891, 862 cm^{-1}. HRMS *m/z* calculated for $C_{21}H_{31}NO_5Na$ (M^+Na) 400.2100, found 400.2102



E/*Z*-**3m**

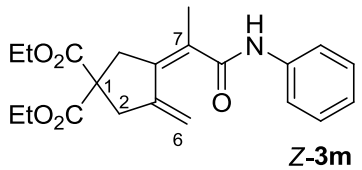
<u>Compounds (*Z*)- and (*E*)-diethyl-3-methylene-4-(1-oxo-1-phenylamino)propan-2-ylidene)cyclopentane-1,1-dicarboxylate (***Z*/*E*-3m**)</u>: General cycloaddition procedure was used with enyne **1c** (50 mg, 0.2 mmol), phenyl isocyanate (23.7 mg, 0.2 mmol) **2b**, $Ni(COD)_2$ (5.5 mg, 0.02 mmol), IPr (15.5 mg, 0.04 mmol) and 2 ml toluene and stirred for 3 h at 80 °C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compounds ***E*-3m** and ***Z*-3m** both as oils (72 mg, 72 %).



E-**3m**

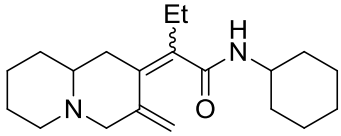
***E*-3m:** ^1H NMR (300MHz, $CDCl_3$): δ (ppm) 8.24 (s, 1H), 7.66 (d, J = 8.1 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.15 (s, 1H), 5.34 (s, 2H), 4.21 (q, J = 7.2 Hz, 4H), 3.14 (s, 4H), 2.16 (s, 3H), 1.25 (t, J = 6.9 Hz, 6H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 171.5, 169.6,

144.2, 138.4, 136.8, 129.4, 129.2, 124.4, 119.9, 114.3, 62.1, 57.4, 41.7, 40.5, 17.8, 14.2. IR (neat): 3299, 2982, 1733, 1654, 1533, 1239, 1074, 904, 861, 757 cm^{-1}. nOe correlation between the vinylic proton on C-6 and the methyl protons on C-7. HRMS *m/z* calculated for $C_{21}H_{25}NO_5Na$ (M^+Na) 394.1630, found 394.1642.



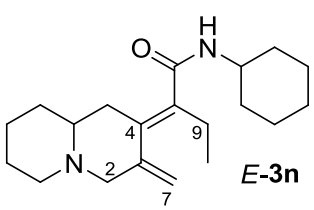
Z-**3m**

***Z*-3m:** ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.52 (d, J = 8 Hz, 2H), 7.34 (t, J = 7.6 Hz, 3H), 7.13 (t, J = 7.2 Hz, 1H), 5.30 (s, 1H), 5.12 (s, 1H), 4.23 (q, J = 7.2 Hz, 4H), 3.06 (s, 4H), 2.31 (s, 3H), 1.27 (t, J = 7.2 Hz, 6H). ^{13}C {^1H} NMR (75 MHz, $CDCl_3$): δ (ppm) 171.3, 169.4, 142.7, 138.2, 136.1, 129.3, 128.3, 124.6, 119.8, 111.9, 62.02, 56.9, 42.3, 39.2, 18.8, 14.2. IR (neat): 3306, 2980, 1731, 1665, 1255, 1194, 1096, 756 cm^{-1}. nOe correlation between the two vinylic protons on C-6. HRMS *m/z* calculated for $C_{21}H_{25}NO_5Na$ (M^+Na) 394.1630, found 394.1639.



E/*Z*-**3n**

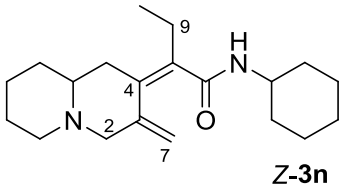
<u>Compounds (*Z*)- and (*E*)-*N*-cyclohexyl-2-(2-methylene-1H-quinolizin-3(2H,4H,6H,7H,8H,9H,9aH)ylidene)butanamide (***Z*/*E*-3n**)</u>: General cycloaddition procedure was used with enyne **1d** (100 mg, 0.52 mmol), cyclohexylisocyanate (65.5 mg, 0.52 mmol) **2b**, $Ni(COD)_2$ (14.30 mg, 0.052 mmol), IPr (40.4 mg, 0.104 mmol) and 5.2 ml toluene and stirred for 3 h at 80 °C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compounds ***E*-3n** as a colorless solid (m.p.172-175 °C) and ***Z*-3n** as an oil (131 mg, 79 %).



E-**3n**

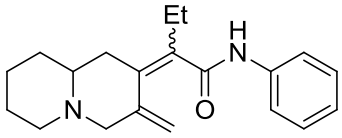
***E*-3n:** ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.76 (m, 1H), 4.98 (s, 1H), 4.79 (s, 1H), 3.85-3.92 (m, 1H), 3.40-3.52 (m,

1H), 2.80-2.85 (m, 1H), 2.57-2.60 (m, 1H), 2.30-2.50 (m, 2H), 2.20-2.25 (m, 1H), 1.93-2.10 (m, 6H), 1.52-1.740 (m, 8H), 1.15-1.43 (m, 6H), 1.01 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.8, 143.8, 134.6, 134.3, 111.9, 63.9, 60.6, 56.1, 48.3, 43.6, 33.4, 32.9, 25.8, 25.7, 25.2, 24.1, 23.9, 13.5. IR (neat): 3372, 2981, 2935, 1727, 1683, 1269, 1039 cm^{-1}. nOe correlation between a vinylic proton on C-7 and the ethyl protons on C-8. HRMS *m/z* calculated for $C_{20}H_{33}N_2ONa$ (M^+Na) 317.2593, found 317.2588.



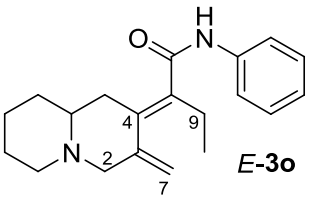
***Z*-3n**

***Z*-3n:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.41-5.39 (m, 1H), 5.05 (s, 1H), 4.80 (s, 1H), 3.60-3.80 (m, 1H), 3.57-3.60 (m, 1H), 3.53 (s, 1H), 2.80-2.92 (m, 1H), 1.8-2.4 (m, 6H), 1.4-1.8 (m, 6H) 0.8-1.4 (m, 8H),. ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 170.2,143.6, 135.7, 133.7, 113.1, 63.4, 57.6, 56.4, 47.6, 42.9, 33.3, 33.1, 25.7, 25.6, 24.8, 24.1, 23.4, 13.2. IR (neat): 3372, 2981, 2935, 1727, 1683, 1269, 1039 cm^{-1}. nOe correlation between the two vinylic protons on C-7. HRMS *m/z* calculated for $C_{20}H_{33}N_2ONa$ (M^+Na) 317.2593, found 317.2593.



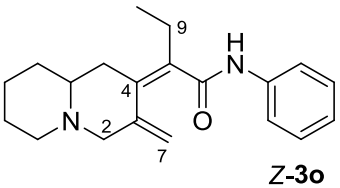
E/*Z*-**3o**

<u>Compounds (*Z*)- and (*E*)-2-(2-methylene)-1H-quinolizin-3(2H,4H,6H,7H,8H,9H,9aH)-ylidene)-*N*-phenylbutanamide (**Z**/***E*-3o**)</u>: General cycloaddition procedure was used with enyne **1d** (100 mg, 0.52 mmol), phenyl isocyanate (62.5 mg, 0.52 mmol) **2b**, $Ni(COD)_2$ (14.30 mg, 0.052 mmol), IPr (40.4 mg, 0.104 mmol) and 5.2 ml toluene and stirred for 3 h at 80 °C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound ***E*-3o** as a colorless solid (m.p. 98 -100 °C) and compound ***Z*-3o** as oil (115 mg, 71 %).



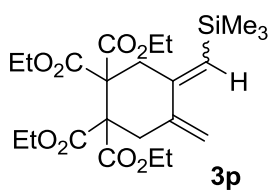
E-**3o**

***E*-3o:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.08 (m, 1H), 7.62 (d, J = 5.7 MHz, 2H), 7.20-7.35 (m, 2H), 7.12 (t, J = 7.2 Hz, 2H), 5.04 (s, 1H), 4.85 (s, 1H), 3.65-3.70 (m, 1H), 2.9-3.1 (s, 1H), 2.81 (d, J= 11.2 Hz, 1H), 2.66 (d, J= 12 Hz, 1H), 2.49-2.58 (m, 2H), 2.31 (m, 1H), 2.01-2.15 (m, 3H), 1.59-1.76 (m, 4H), 1.24 -1.56 (m, 2H), 1.09 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 169.6, 144.0, 138.5, 129.6, 124.8, 120.4, 112.3, 64.4, 61.0, 56.4, 44.0, 33.3, 26.0, 24.4, 24.4, 14.0. IR (neat): 3275, 2930, 2798, 1672, 1590, 1539, 1250, 735, 690 cm^{-1}. nOe correlation between a vinylic proton on C-7 and the ethyl protons on C-8. HRMS *m/z* calculated for $C_{20}H_{27}N_2O$ (M^+Na) 311.2123, found 311.2124.



Z-**3o**

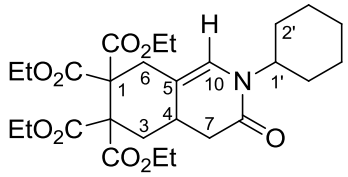
***Z*-3o:** ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.43-7.55 (m, 3H), 7.29 (d, J = 7.2 Hz, 2H), 7.05-7.09 (m, 1H), 5.06 (t, J = 2 Hz, 1H), 4.85 (m, 1H), 3.61 (d, J = 12.4 Hz, 1H), 2.95-3.0 (m, 1H), 2.55-2.61 (m, 1H), 1.90-2.46 (m, 4H), 1.45-1.80 (m, 4H), 1.05-1.20 (m, 6H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): 169.9, 143.8, 138.6, 135.4, 135.4, 129.1, 124.3, 119.8, 113.4, 63.3, 57.6, 56.4, 42.7, 33.1, 25.7, 24.1, 23.5, 13.4. IR (neat): 3285, 2935, 2798, 1662, 1598, 1539, 1247, 907, 732, 693 cm^{-1}. nOe corelation between the two vinylic protons on C-7. HRMS *m/z* calculated for $C_{20}H_{27}N_2O$ (M^+Na) 311.2123, found 311.2122.



3p

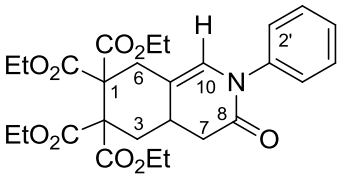
<u>Synthesis of (*E*)-tetraethyl-2-butyryl-4-methylene-5[(trimethyl silyl)methylene)]cyclohexane-1,1,2-tricarboxylate (**3p**)</u>: General cycloaddition procedure was used with enyne **1e** (50 mg, 0.11 mmol) and cyclohexylisocyanate **2a** (13.35 mg, 0.11 mmol), $Ni(COD)_2$ (3.0 mg, 0.011

mmol), IPr (8.54 mg, 0.022 mmol) and stirred for 24 h at 100 °C. The crude compound was purified by column chromatography eluting with 30 % EtOAc/hexanes to yield compound **3p** as an oil (13.8 mg, 31 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.24 (s, 1H), 5.94 (s, 1H), 5.12 (s, 1H), 5.03 (s, 1H), 4.18 (m, 8H), 2.16 (s, 3H), 1.73 (s, 2H), 1.21-1.29 (m, 12H), 0.03 (s, 9H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm). 169.3, 139.0, 136.8, 120.7, 113.6, 62.0, 61.9, 60.3, 36.3, 29.9, 22.5, 14.0, -0.9 ppm. HRMS m/z calculated for $C_{23}H_{36}O_8NaSi$ (M^+Na) 491.2077, found 491.2071.



10

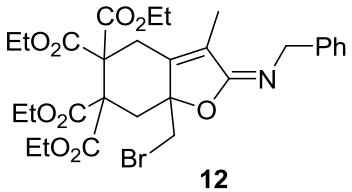
Synthesis of tetraethyl-2-cyclohexyl-3-oxo-3,4,4a,5-tetra hydroisoquinoline-6,6,7,7(2H,8H)-tetracarboxylate (**10**): General cycloaddition procedure was used with enyne **1f** and cyclohexylisocyanate (31.6 mg, 0.25 mmol) **2a**, $Ni(COD)_2$, IPr, and toluene stirring for 4 h at 80 °C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound **10** as an oil (9.5 mg, 15 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.89 (s, 1H), 4.0-4.3 (m, 8H), 3.4-3.6 (m, 1H), 2.8-3.0 (m, 2H), 2.5-2.6 (m, 4H), 1.8-2.0 (m, 2H), 1.5-1.8, 1.0-1.2 (m, 6H), 1.2-1.4 (m, 14H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 170.6, 170.4, 168.9, 168.9, 167.6, 120.4, 114.6, 62.3, 62.1, 61.9, 61.7, 59.3, 51.5, 49.3, 38.8, 36.2, 34.2, 33.8, 31.7, 30.8, 29.9, 28.8, 25.9, 25.8, 14.2, 14.1 14.0 ppm. nOe correlation between the vinylic protons on C-10 with a) protons on the cyclohexyl ring, and b) protons on C-10. HRMS calculated for $C_{27}H_{33}NO_9Na$ (M^+Na) 538.2053, found 538.2061.



11

Synthesis of tetraethyl-3-oxo-2-phenyl-3,4,4a,5-tetrahydroisoquinoline-6,6,7,7(2H,8H)-tetracarboxylate **11**:

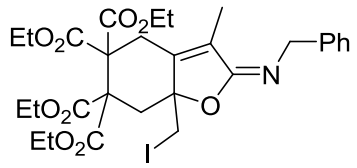
General cycloaddition procedure was used with enyne **1f** (100 mg, 0.25 mmol), phenyl isocyanate (30.1 mg, 0.25 mmol), $NiCOD_2$ (6.87 mg, 0.025 mmol), IPr (19.4 mg, 0.050 mmol) and toluene 2.5 ml were stirred for 4 h at 80 °C. The crude compound was purified by flash chromatography eluting with 30 % EtOAc/hexanes to yield compound **11** as an oil (25.4 mg, 19 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.39 (t, J = 7.2 Hz , 2H), 7.23-7.29 (m, 3H), 6.09 (s, 1H), 4.17-4.32 (m, 8H), 2.76-2.93 (m, 4H), 2.61-2.50 (m, 2H), 2.26-2.30 (m, 1H), 1.18-1.38 (m, 12H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ (ppm) 171.6, 169.7, 144.2, 138.4, 136.8, 129.5, 129.2, 124.4, 119.9, 114.3, 62.1, 57.5, 41.8, 40.6, 17.9, 14.2. nOe correlation between the vinylic proton on C-10 and a) phenyl protons and b) protons on C-6. HMBC correlation between the vinylic proton on C-10 and a) C-8, b) C-6, and c) C-1'. HRMS *m/z* calculated for $C_{28}H_{41}NO_9Na$ (M^+Na) 544.2523, found 544.2514



12

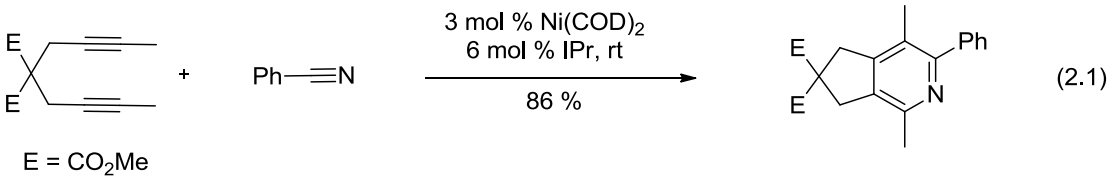
(*E*)-tetraethyl-2-(benzylimino)-7a-(bromomethyl)-3-methyl-7,7'-dihydrobenzofuran-5,5,6,6(2H,4H)-tetracarboxylate (**12**): Compound **12** were prepared as described by Wang and co-workers.[8] Under nitrogen atmosphere, dienamide ***Z*-3b** (83 mg, 0.15 mmol), *N*-bromosuccinimide (27.2 mg, 0.15 mmol) and 1.5 ml THF were stirred at room temperature for 3 h. The reaction mixture was quenched with deionized water and extracted twice with dichloromethane (10 ml x 2 times). After drying the organic layer with $MgSO_4$, the crude product was isolated and purified by flash chromatography (30 % ethyl acetate/ hexanes) to obtain compound **12** (50 mg, 53 %) as an oil. ^{1}H NMR (400 MHz, C_6D_6) δ (ppm). 7.58-7.59 (s, 2H), 7.21 (t, J = 8.0 Hz, 2H), 7.11 (d, J = 7.2 Hz, 1H), 4.82 (dd, J = 15.0, 2.5 Hz, 2H), 3.80-4.11 (m, 8H), 3.1-3.6 (m, 6H), 1.79 (s, 3H), 0.86-

1.1 (m, 12H) ^{13}C {^{1}H} NMR (75 MHz, C_6D_6): δ (ppm) 170.3, 169.4, 162.2, 145.9, 142.2, 131.1, 128.9, 128.8, 127.9, 127.0, 85.6, 26.8, 62.6, 62.4, 61.5, 60.1, 52.0, 39.2, 30.6, 29.9, 29.2, 29.2, 14.1, 9.9. HRMS *m/z* calculated for $C_{29}H_{37}NO_9Br$ (M^+H) 622.50, found 622.1652.

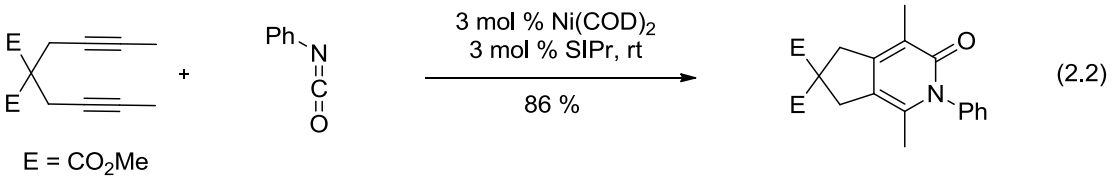


13

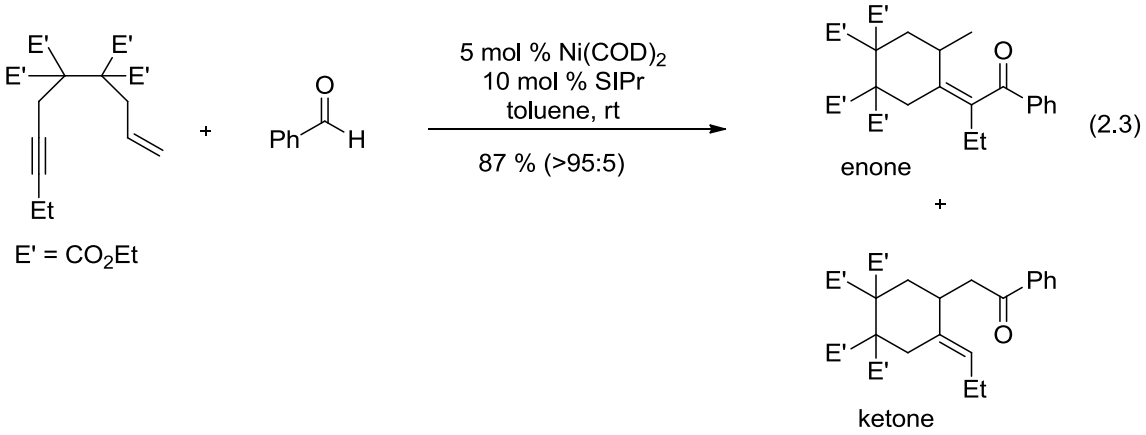
(*E*)-tetraethyl-2-(benzylimino)-7a-(iodomethyl)-3-methyl -7,7'-dihydrobenzofuran-5,5,6,6(2H,4H)-tetracarboxylate (**13**): Compound **13** was prepared as described by Wang and co-workers.[8] Under nitrogen atmosphere, compound ***Z*-3b** (30 mg, 0.06 mmol), iodine (16.8 mg, 0.07 mmol), and dichloromethane (0.6 ml) were stirred at room temperature for 8 h. The reaction was quenched with 1 ml deionozed water and extracted with dichloromethane (5 ml x 2). The organic layers were dried over $MgSO_4$. The crude product was isolated and purified using silica gel flash chromatography with 30 % ethyl acetate/ hexanes to yield compound **13** (33.6 mg, 90 %) as an oil. ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 7.58-7.59 (s, 2H), 7.21 (t, J = 8.0 Hz, 2H), 7.11 (d, J = 7.2 Hz, 1H), 4.82 (dd, J = 15.0, 2.5 Hz, 2H), 3.80-4.11 (m, 8H), 3.1-3.6 (m, 6H), 1.79 (s, 3H), 0.86-1.1 (m, 12H). ^{13}C {^{13}H} NMR (75 MHz, $CDCl_3$): 170.3, 169.4, 162.2, 145.9, 142.2, 131.1, 128.9, 128.8, 127.9, 127.0, 85.6, 62.8, 62.6, 62.3, 61.5, 60.1, 52.0, 39.2, 30.6, 30.3, 30.3, 29.9. 29.2, 14.1, 9.9. HRMS calculated for $C_{29}H_{37}NO_9I$ (M^+H) 670.14, found 670.1497.


E
E
E = CO2Me
Ph—≡N
3 mol % Ni(COD)2
6 mol % IPr, rt
86 %
Ph
N

(2.1)


E
E
E = CO2Me
Ph
N
C
O
3 mol % Ni(COD)2
3 mol % SIPr, rt
86 %
O
N
Ph

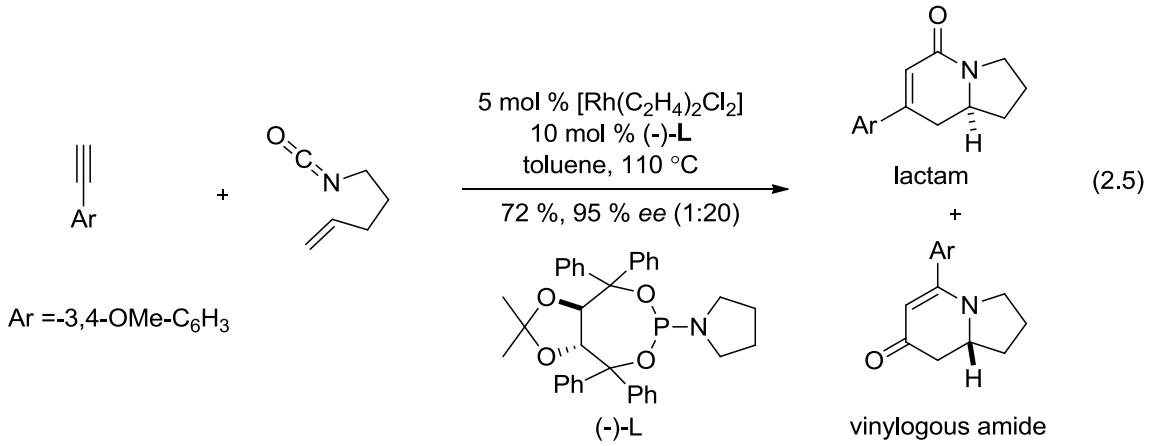
(2.2)


E'
E'
E'
E'
Et
E' = CO2Et
O
Ph
H
5 mol % Ni(COD)2
10 mol % SIPr
toluene, rt
87 % (>95:5)
E'
E'
E'
E'
O
Ph
Et
enone
+
E'
E'
E'
E'
Ph
O
Et
ketone

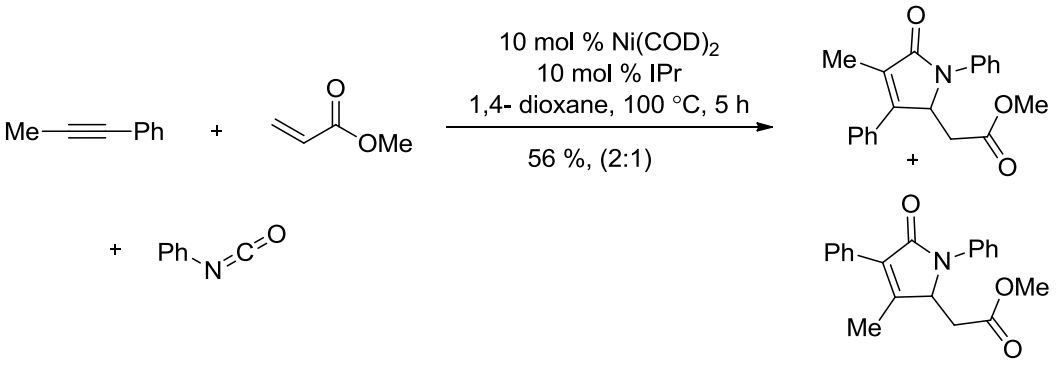
(2.3)


E
R'
E
+
R
N=C=O
[M]
"
R'
E
O
E
N
R
"
E = CO2Me

(2.4)


Ar
+
O
C
N
5 mol % [Rh(C2H4)2Cl2]
10 mol % (-)-L
toluene, 110 °C
72 %, 95 % ee (1:20)
Ar =-3,4-OMe-C6H3
Ph
Ph
O
O
P
N
O
O
Ph
Ph
(-)-L
O
N
Ar
H
lactam
+
Ar
N
O
H
vinylogous amide

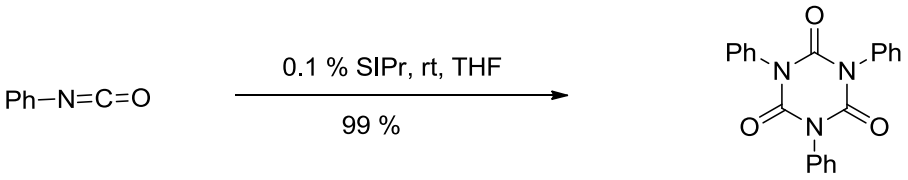
(2.5)


Me
Ph
+
O
OMe
+
Ph
N
C
O
10 mol % Ni(COD)2
10 mol % IPr
1,4- dioxane, 100 °C, 5 h
56 %, (2:1)
O
Me
N
Ph
OMe
Ph
O
+
O
Ph
N
Ph
OMe
Me
O

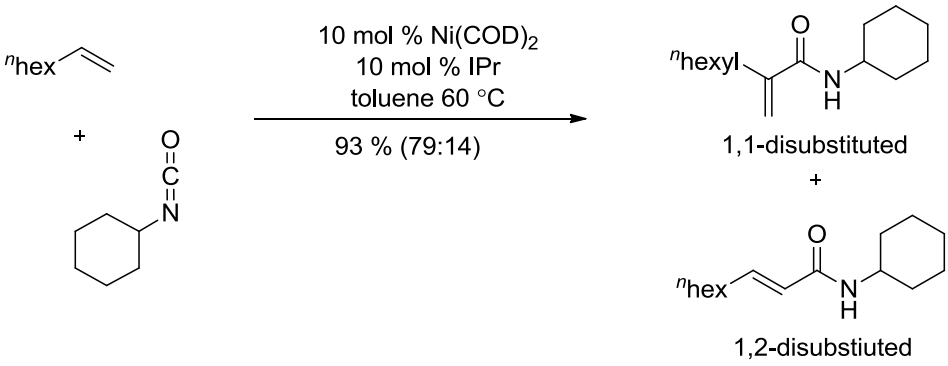
(2.6)


E'
E'
E'
E'
E' = CO2Et
5 mol % Ni(COD)2
10 mol % IDTB,
60 °C, toluene
90 %
E'
E'
E'
E'

(2.7)

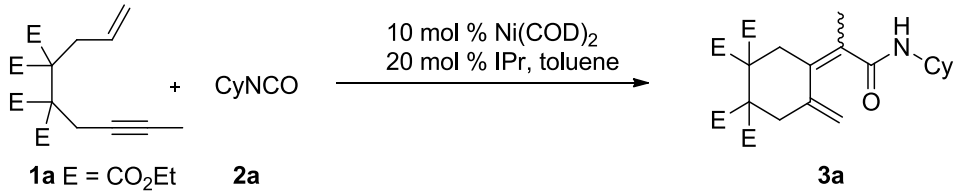

Ph–N=C=O
0.1 % SIPr, rt, THF
99 %
Ph
N
O
Ph
N
O
N
O
Ph

(2.8)


nhex
+
O
C
N
10 mol % Ni(COD)2
10 mol % IPr
toluene 60 °C
93 % (79:14)
nhexyl
O
N
H
1,1-disubstituted
+
nhex
O
N
H
1,2-disubstiuted

(2.9)

Table 2.10 Nickel catalyzed cycloaddition of enyne **1a** and cyclohexylisocyanate **2a**



(2.10)

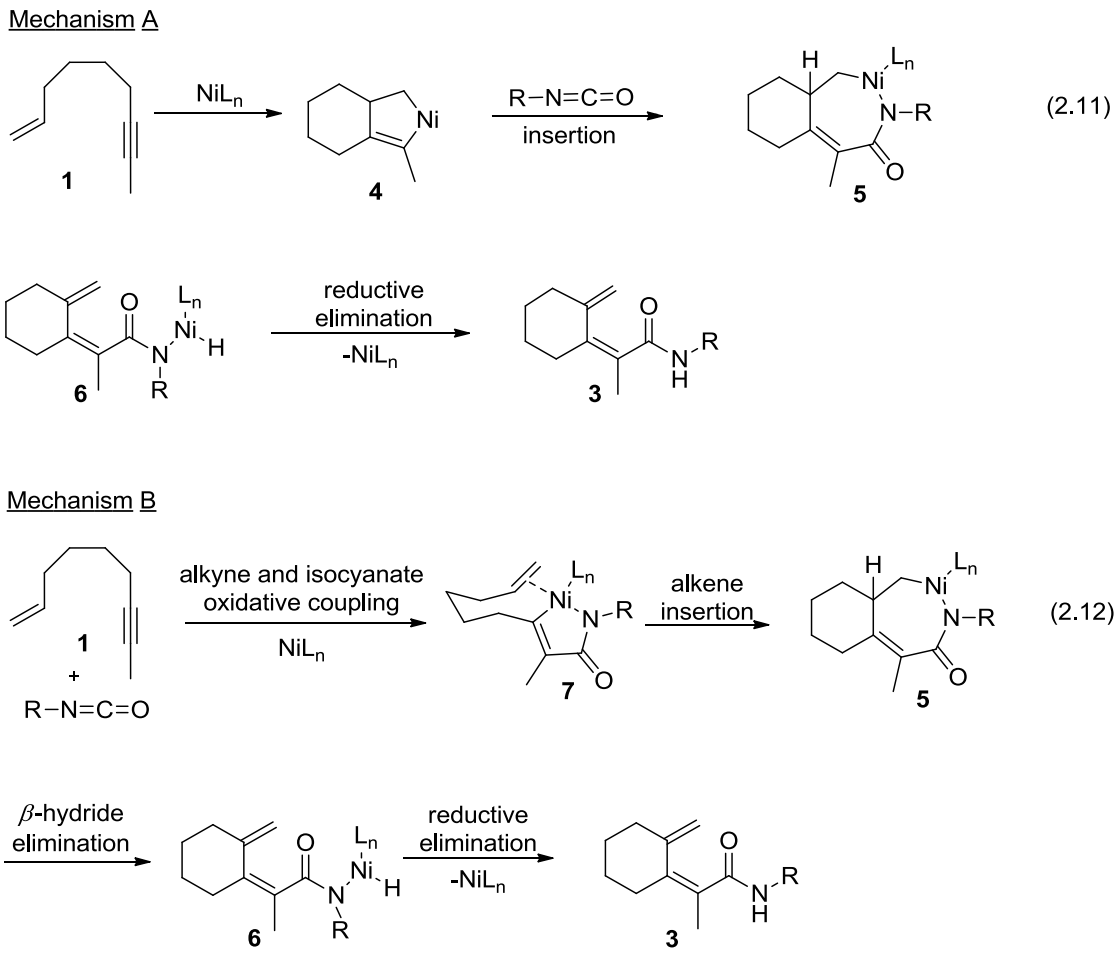
1a E = CO_2Et **2a** **3a**

entry	ligand	% conversion of **1a**[b]	% yield of **3a**[b]
1	none	10	nd
2	P(*n*-Bu)$_3$	31	nd[c]
3	PPh_3	17	nd
4	P(*p*-Tol)$_3$	31	nd
5	DPPF	7	nd
6	BINAP	5	nd
7	biphenP(*t*-Bu)$_2$	17	nd
8	I*t*Bu	14	nd
9	IMes	33	nd
10	SIPr	90	78
11	IPr	100	80

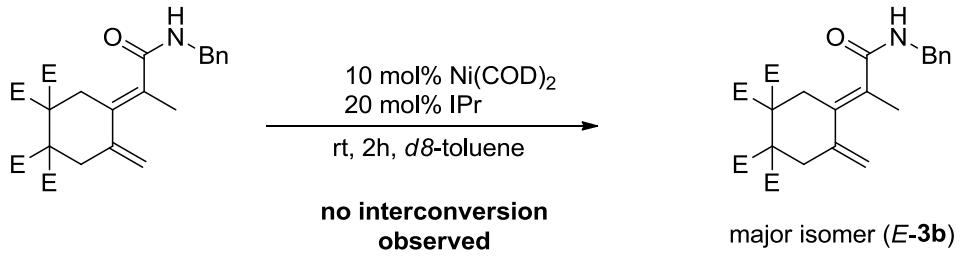
[a] Reaction conditions: 10 mol % Ni(COD)$_2$, 20 mol % ligand, 0.1 M **1**, 0.11 M **2a**, toluene, room temperature, 17h.

[b] Determined by GC using naphthalene as an internal standard.

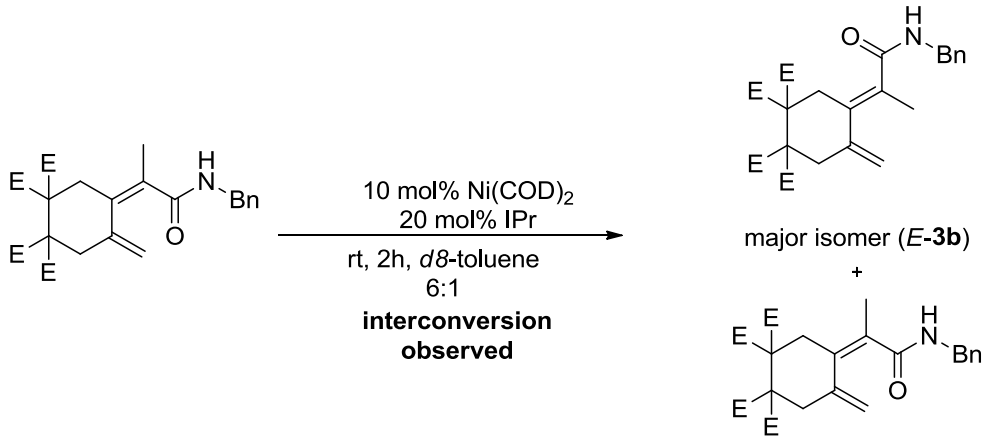
[c] nd = not detectable by GC.



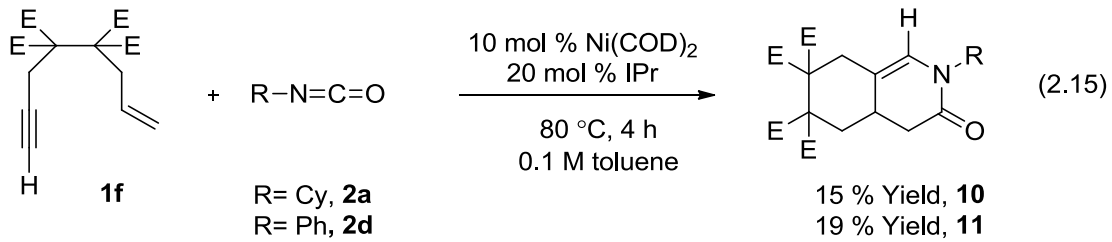
Scheme 2.1 Possible mechanisms for dienamide formation


10 mol% Ni(COD)2
20 mol% IPr
rt, 2h, d8-toluene
no interconversion observed
major isomer (E-3b)

(2.13)

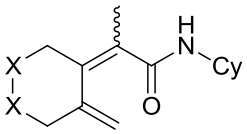
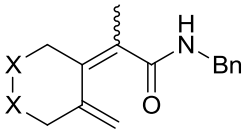
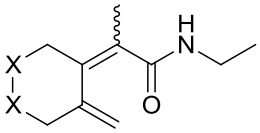
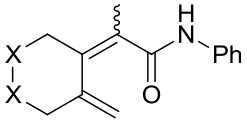
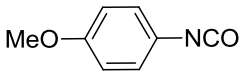
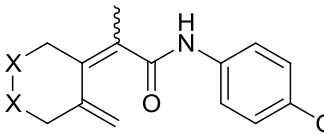
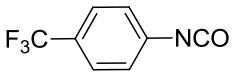
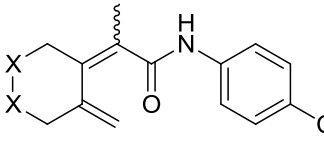
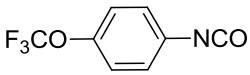
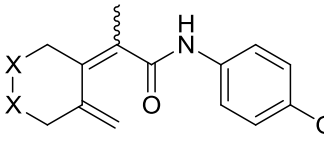
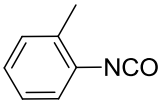
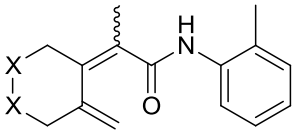
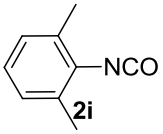
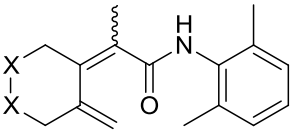

10 mol% Ni(COD)2
20 mol% IPr
rt, 2h, d8-toluene
6:1
interconversion observed
major isomer (E-3b)
+
minor isomer (Z-3b)

(2.14)


E
E
E
E
H
1f
+
R−N=C=O
R= Cy, 2a
R= Ph, 2d
10 mol % Ni(COD)2
20 mol % IPr
80 °C, 4 h
0.1 M toluene
H
E
E
N
R
E
E
O
15 % Yield, 10
19 % Yield, 11

(2.15)

Table 2.2 Dienamide formation from enyne **1a** and isocyanate **2a-2i**

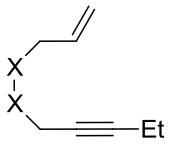
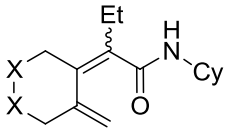
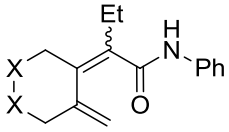
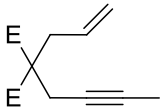
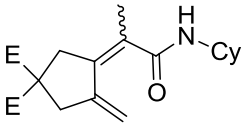
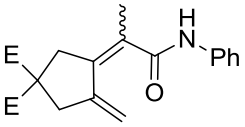
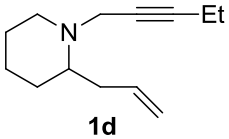
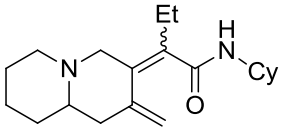
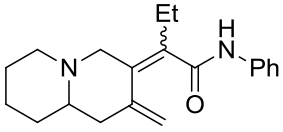
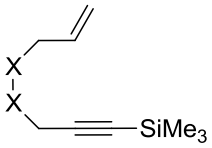
entry	isocyanate	*E*/*Z* products		reaction time	*E*:*Z* ratio[a]	% yield[b]
1	CyNCO **2a**		**E/Z-3a**	rt, 1 h	5:1	70
2	BnNCO **2b**		**E/Z-3b**	rt, 2h	2:1	68
3	EtNCO **2c**		**E/Z-3c**	80 °C, 1 h	2:1	80
4	PhNCO **2d**		**E/Z-3d**	60 °C, 2 h	2:1	79
5	 **2e**		**E/Z-3e**	60 °C, 2 h	2:1	74
6	 **2f**		**E/Z-3f**	100 °C, 7 h	1.8:1	57
7	 **2g**		**E/Z-3g**	80 °C, 5 h	2:1	66
8	 **2h**		**E/Z-3h**	80 °C, 1 h	2:1	71
9	 **2i**		**E/Z-3i**	80 °C, 1.5 h	2:1	80

Reaction condns: 1 equiv. **1**, 1 equiv. **2**

[a] Determined by ^{1}H-NMR, [b] isolated yields, average of 2 runs

X = $[C(CO_2Et)]_2$

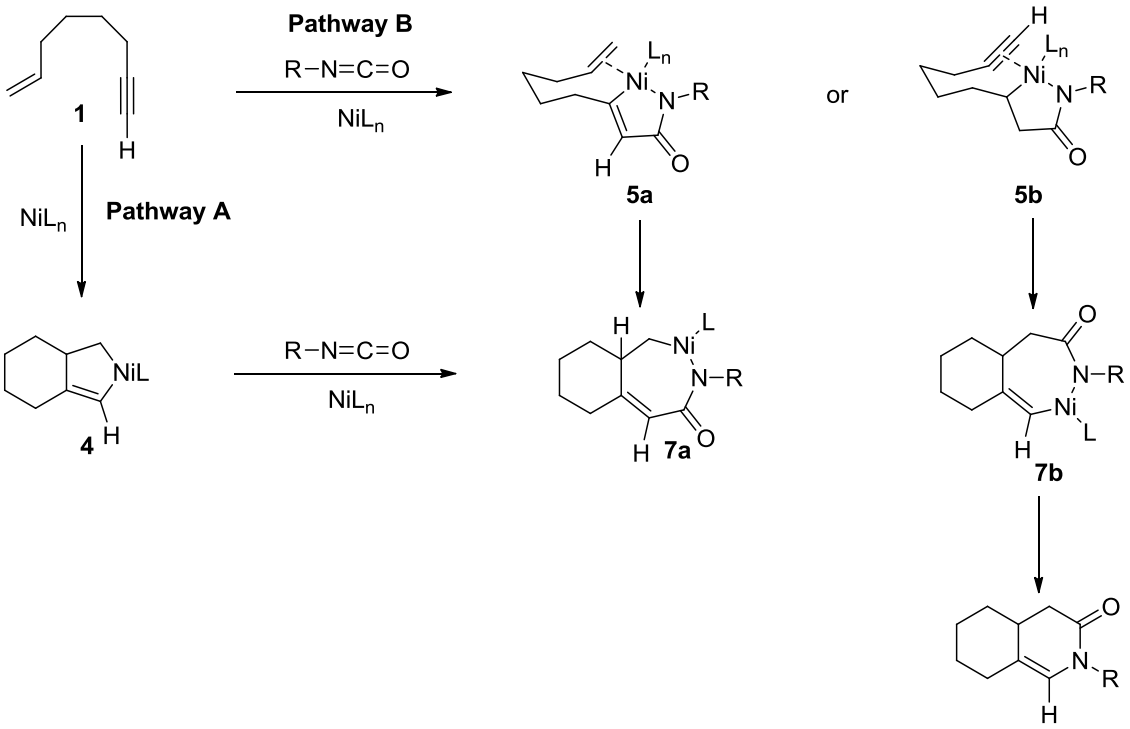
Table 2.3 Substrate scope using enynes **1b**-**1d** and isocyanates **2a** and **2b**

entry	enyne	isocyanate	*E*, *Z* products	reaction time	*E*:*Z* ratio[a]	% yield[b]
1	 X = $[C(CO)_2Et]_2$ **1b**	CyNCO **2a**	 *E*/*Z*- **3j**	rt, 4 h	4:1	89
2	**1b**	PhNCO **2d**	 *E*/*Z*-**3k**	rt, 6 h	4:1	89
3	 E = CO_2Me **1c**	**2a**	 *E*/*Z*-**3l**	80 °C, 4 h	4:1	65
4	**1c**	**2d**	 *E*/*Z*-**3m**	80 °C, 3 h	4:1	72
5	 **1d**	**2a**	 *E*/*Z*-**3n**	80 °C, 3h	1.4:1	72
6	**1d**	**2d**	 *E*/*Z*-**3o**	80 °C, 3 h	1.4:1	72
7	 **1e**	**2a/2d**	no dienamide product isolated			

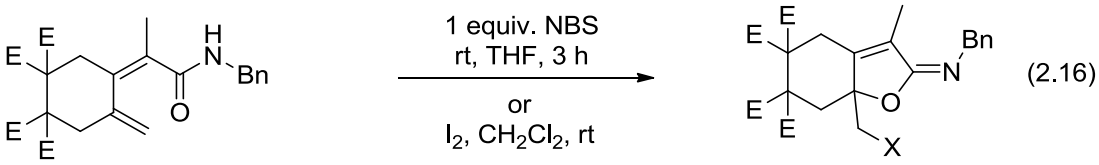
Reaction condns: 0.1 M enyne, 0.11 M isocyanate, 0.1 M toluene

[a] determined by ^1H NMR

[b] isolated yields, average of 2 runs



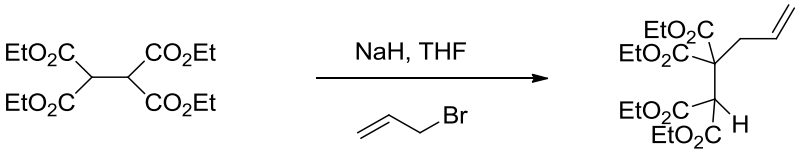
Scheme 2.3 Possible mechanism for lactam formation



(2.16)

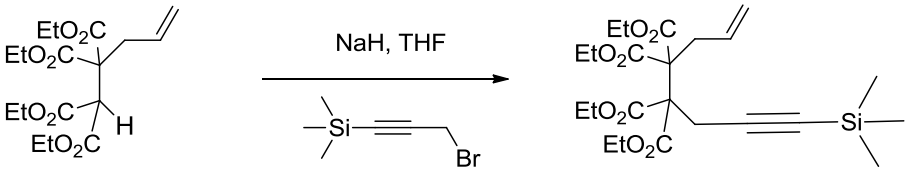
Z-**3b**

X = Br, **12**, 53 % Yield
X = I, **13**, 90 % Yield



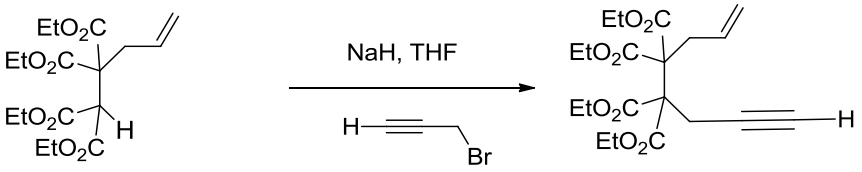
(2.17)

14



14 **1e**

(2.18)



14 **1f**

(2.19)

References

1. Reviews of cycloaddition : (a) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. b) Chopade, P.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. c) Schore, N. *Chem. Rev.* **1988**, *88*, 1081. d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, 104, 2127. e) Varela, J. A.; Saá, C. *Synlett.* **2008**, 2571.

2. Trost, B. M. *Science*, **1991**, *254*, 1471.

3. a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc.* **2005**, *127*, 5030; b) Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J. *J. Org. Chem.* **2006**, *71*, 5834.

4. a) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (b) Duong, H. A.; Louie, J. *J. Organomet. Chem.* **2005**, *690*, 5098. (c) Duong, H. A.; Louie, J. *Tetrahedron* **2006**, *62*, 7547.

5. a) Tekavec, T. N.; Louie, J. *Org. Lett.* **2005**, *7*, 4037. (b) Tekavec, T. N.; Louie, J. *J. Org. Chem.* **2008**, *73*, 2641.

6. a) Williams, R.; Manka, J. T.; Rodriguez, A. L.; Vinson, P. N.; Niswender, C. M.; Weaver, D. C.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1350. b) Dow, R. L.; Carpino, P. A.; Hadcock, J. R.; Black, S. C.; Iredale, P. A.; DaSilva-Jardine, P.; Schneider, S. R.; Paight, E. S.; Griffith, D. A.; Scott, D. O.; O'Connor, R. E.; Nduaka, C. I. *J. Med. Chem.* **2009**, *52*, 2652.

7. Yu, T. R.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782-2783. (b) Yu, T. R.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370-12371. (c) Lee, E. E.; Rovis, T. *Org. Lett.* **2008**, *10*, 1231-1234. (d) Ozawa, T.; Horie, H.; Kurahashi, T.; Matsubara, S. *Chem. Commun.*, 2010, **46**, 8055-8057.

8. a) Tekavec,T. N.; Louie, J. *Tetrahedron* **2006**, *64*, 6870. b) Duong, H. A.; Cross, M. J.; Louie, J. *Org. Lett.* **2004**, *6*, 4679.

9. Scleicher, K. D.; Jamison, T. *Org. Lett.* **2007**, *9*, 875-878.

10. Koo, K.; Hillhouse, G. *Organometallics* **1995**, *14*, 4421-4423.

11. Wang, C.; Lu, J.; Mao, G.; Xi, Z. *J. Org. Chem.* **2005**, *70*, 5150.

12. (a) Böhm, V. P. W.; Gstüttmayr, C. W. K., Weskamp, T.; Herrmann, W. A. *Angew*. *Chem*. *Int*. *Ed*. **2001**, *40*, 3387. (b) Arduengo, A. J. III; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J. Unverzagt, M. *Tetrahedron* **1999**, *55*, 14523. (c) Böhm, V. P. W.; Weskammp, T.; Gstottmayr, W. K.; Herrmann, W. A. *Angew*. *Chem*. *Int*. *Ed*. **2000**, *39*, 1602. (d) Jensen, D. R.; Sigman, M. S. *Org*. *Lett*. **2003**, 5, 63.

13. Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J*. *Org*. *Chem*. **1994**, *59*, 284.

CHAPTER 3

IRON-CATALYZED CYCLOADDITION OF ALKYNENITRILES AND ALKYNES

Introduction

Pyridine[1] rings are common in various natural products and bioactive compounds.[2,3] Synthetic methods that provide a rapid and efficient pathway for the synthesis of such rings would be useful. A reported methodology for the synthesis of pyridine rings involves the [2+2+2] cycloaddition reaction of alkynes and nitriles.[3] Various metals such as Co,[4] Rh,[5] Ru,[6] and Ni[7] have been utilized as catalysts to synthesize diversely substituted pyridine rings in these methods. Another approach to construction of pyridine rings with different substitution patterns is by the cycloaddition of alkynenitriles and alkynes. Seminal work in this field was demonstrated by Vollhardt[4b] (Figure 3.1, Equation 3.1-3.3). The reaction of a tethered alkyne and the nitrile with an alkyne afforded pyridines in moderate to good yields with $CpCo(CO)_2$. The pyridine product was obtained in good yields when symmetrical alkynes are used in the cycloaddition (Equation 3.1). Poor regioselectivity were observed for the pyridine product when unsymmetrical alkynes were used in the cycloaddition (Equations 3.2-3.3). The reaction

also requires the slow addition of the alkynenitrile and alkyne over a 4-5 h time period using a syringe pump. The other drawback of this method is that the cobalt-catalyst requires ultra-violet light for activation. Saá[4f] extended the substrate scope with the same $CpCo(CO)_2$ catalyst system as that used by Vollhardt to synthesize annelated bipyridines (Equation 3.4), and terpyridines (Equation 3.4) albeit in low yields. *Spiro*-pyridines[4e] can also be prepared (Equation 3.5) using catalytic $CpCo(CO)_2$ albeit in low yields and low selectivity. Microwaves can also be used to prepare tetrahydronaphthyridines[4d] by reacting dialkynenitriles in the presence of $CpCo(CO)_2$ catalyst (Equation 3.6). Interestingly, tantalum[8] has been utilized in the cycloaddition reaction of alkynenitriles and alkynes to form pyridines. However, this cycloaddition reaction has been applied to only one substrate and the reaction required stoichiometric amounts of tantalum hexachloride. With all these transition metals been used in the cycloaddition reactions, there is a need to use cost-effective, environmentally less-toxic, and easily available metal salts. Therefore, a mild and effective catalyst system for the cycloaddition of alkynenitriles and alkynes is highly desired.

Replacing the use of precious metals in catalysis with more abundant and potentially less-toxic metal complexes is highly desrired. Iron salts are easily available, cost effective, and less-toxic that other transition metal complexes thus making it an attractive alternative as a catalyst. The majority of the use of iron in catalysis has been in cross coupling,[9] oxidation,[10] and polymerization.[9] Only in the last decade Fe-catalyst systems have been demonstrated in [2+2+2] cycloaddition chemistry. The cyclotrimerization of alkynes represents the majority of the [2+2+2] cycloaddition reaction examples. Okamoto[12a] used a combination of iron chloride and IPr as the catalyst to synthesize a

tricyclic benzene derivative in moderate to good yields (Equation 3.7). Breshi[12b] and co-workers developed a Fe-cyclohexatriene-cyclooctadiene [Fe(CHT)(COD)] complex. This complex was used in the intermolecular cycloaddition of alkynes affording benzene products (Equation 3.8). The major drawback to this method is the tedious preparation of the Fe-complex. Fürstner[12c] developed a very effective iron catalyst for the cyclotrimerization of alkynes (Equation 3.9). Cyclized products were obtained in good yields. However, the reactivity of this iron catalyst was demonstrated with only alkenes and alkynes.

There are very few examples that are reported for synthesizing pyridines using iron by cycloaddition reactions. The very first example of the use of iron in pyridine synthesis was reported by Sir William Ramsay[13] in 1872 (Figure 3.1). He synthesized pyridine in traces by passing hydrocyanic acid and acetylene through a red hot iron tube. It was not until 1996 that Knoch[14a] isolated a phosphorane-cyclooctadiene-iron complex and used it in the synthesis of pyridine derivatives from alkynes and nitriles (Equation 3.10). Although the cycloaddition reaction required low catalyst loading, along with the desired pyridine products, significant cyclotrimerization of the alkyne was also observed. Ferré[14b] designed an ironpentamethyl(cyclopentadienyl)acetonitrile sandwich complex that successfully afforded pyridine product in 73 % yield (Equation 3.11). However, this cycloaddition reaction required stoichiometric amounts of the iron-complex and was limited to one activated alkyne. Wan[14c] has reported an iron-catalyzed cycloaddition of diynes and unactivated nitriles (Equation 3.12). Excellent yields were obtained for the pyridine product. However, the reaction requires a large excess of nitrile for the cycloaddition reaction. To the best of our knowledge, these examples represent the only

examples of Fe being used as a catalyst in the preparation of pyridine rings. We were interested in developing an iron catalyst system to synthesize pyridines and expanding on the existing substrate scope in the cycloaddition of alkynenitriles and alkynes.

Results and Discussion

The efficiency of previous iron-catalyzed cycloaddition reactions to generate benzannulated compounds prompted us to investigate the cycloaddition of alkynenitriles and alkynes to synthesize pyridines. We inferred that the difficulty in preparation of pyridines from diynes may be due to the limited reactivity of the nitrile to undergo cycloaddition reactions. Therefore, we strategically chose to tether the alkyne and the nitrile to promote the initial cycloaddition of the alkyne, nitrile, and Fe-catalyst moities. The first step in our study involved the evaluation of various ligands in their ability to bind to Fe and generate an efficient catalyst. Alkynenitrile **1a** and decyne **2a** were subjected to 30 mol % iron acetate and 40 mol % ligand, and zinc dust in DMA at 80 °C. Various ligands such as amines, phosphines, and NHCs were used based on their successful application as ligands in other cycloaddition reactions involving iron.[12] However, the use of phosphines or NHCs as ligands did not result in the formation of the desired cycloaddition pyridine product. Only the unreacted alkynenitrile **1a** was observed by gas chromatography (GC). We then turned our attention to imino-based ligands such as 1,2-diimine and di(imino)pyridine[15,16] ligands. Low or no pyridine product was detected by GC with diimine ligands L1-L5 (Table 3.1, entries 1-5). The 1,2-diimine ligand **L6** afforded the pyridine product (Table 3.1, entry **6)** with 47 % yield

by gas chromatography and 30 % isolated yield. Chirik and other research groups have demonstrated that iron-bis(imino)pyridyl[15, 16] complexes are effective in polymerization reactions. Hence, we evaluated the use of various bis(imino)pyridyl ligands in this cycloaddition reaction in order to obtain higher yields for the desired pyridine product. In our study, low conversions of starting material with no formation of pyridine product was observed in the presence of ketimine-based bis(imino)pyridine ligands (Table 3.1, entries 7-8). On the other hand, reactions involving the use of pyridyl bis(aldimino)pyridine derivatives as ligands gave promising results. The complete conversion of alkynenitrile **1a** was observed by GC in the presence of ligand **L9**, with a yield of 84 % of the desired pyridine product. Increasing the steric bulk of the ligand by using **L10** (Table 3.1, entry 9) had a deleterious effect on the reaction with low conversions of starting material and formation of trace amounts of pyridine product. Interestingly the insertion of an electron-donating group (i.e. –OBn) on to the para position of the aryl ring of the ligand (**L11**) had a profound effect on the reaction outcome. In the presence of **L11** as ligand, the pyridine product was obtained in 62 % yield with lower catalyst loading (entry 11). Gratifyingly, reactions run with **L12** as ligand provided 95 % pyridine product with 20 mol % catalyst loading. In contrast to the trend observed for neutral ligands, an increase in steric hindrance led to an increase in yield (entries 9-10 v/s entries 11-12, respectively). Control reactions were also performed in the absence of $Fe(OAc)_2$, ligand, or Zn successively. These control reactions resulted in no pyridine product formation. Lowering the catalyst loading and switching solvents from DMA to DMF ultimately led to the following optimum reaction conditions: 10 mol % $Fe(OAc)_2$, 13 mol %

bis(aldimine) pyridyl ligand **L12**, 0.4 M alkynenitrile, and 0.4 M alkyne in DMF at 85 °C (Equation 3.13)

The cycloaddition of alkynenitriles and alkynes is a general reaction as a variety of alkynenitriles and alkynes can be used as substrates (Table 3.1). The reaction of alkynenitriles **1a** and **1b** with 5-decyne **2a** afforded good isolated yields of the pyridine products with alkynenitrile **1b** affording slighlty higher yields (Table 3.2, entries 1-2). Similarly, the reaction of phenyl-substituted alkynenitrile **1c** also afforded the corresponding pyridine in good yield (entry 3). Although the cycloaddition of terminal alkynenitrile **1d** resulted in low yield (Table 3.2, entry 4), reasonable yields were obtained when TMS-substituted alkynenitrile **1e** was employed (Table 3.2, entry 5). Next, the substrate scope of alkynes in this reaction was studied. Not surprisingly, 3-hexyne (**2b**) is an effective alkyne substrate (Table 3.2, entry 6). The cycloaddition of diphenylacetylene **2c** and alkynenitrile **1a** requires 2 equiv. of **2c** to afford the pyridine product in appreciable yield (Table 3.2, entry 7) due to competing cyclotrimerization of the alkyne. Alkynenitriles containing either an oxygen or a nitrogen backbone (**1f**, **1g**, and **1h**) also react with decyne **2a** to afford the pyridine product, albeit in moderate yields (Table 3.2, entries 8 and Table 3.3, entries 1 and 2). In contrast, alkynenitrile **1h**, which possesses an all-carbon backbone, reacted with decyne **2a** and afforded better yields of the pyridine cycloaddition product (Table 2.3, entry 3). A tricyclic indenylpyridine was prepared in good yield from the coupling of **1j** and **2b** (Table 2.3, entry 4). In addition, the reaction of 1,6-alkynenitrile **1k**, which possesses a 6-carbon chain tether affords pyridine product **3k**, albeit in lower yields than the corresponding 1,5-alkynenitrile (Table 3.3, entry 5 vs. Table 3.2, entry 1, respectively).

Unsymmetrical alkynes were also employed as coupling partners in the cycloaddition reaction (Table 3.4, equation 3.14). Methyl phenyl acetylene **2d** and alkynenitrile **1a** afford the pyridine product with 1.2:1 ratio of regioisomers (Table 3.4, entry 1). With the regioisomer having the phenyl group distal to the pyridine nitrogen slightly favored. Interestingly, changing the electronics on the phenyl ring improved the regioselectivity. Aryl-alkyl alkyne **2f** possesing an electron withdrawing group ($-CF_3$) (Table 3.4, entry 3) at the para position of the phenyl ring of alkyne **2f** affords a higher ratio of the major regioisomer where the phenyl ring is distal from the pyridine nitrogen as compared to an alkyne **2g** possessing an electron donating group (-OMe) at the para position of the phenyl ring (Table 3.4, entry 2). The reaction of alkynenitrile **1a** and alkyne **2g**, possessing a pyridyl substituent, affords better selectivity where the aryl ring is distal to the pyridine nitrogen as the major regioisomer (Table 3.4, entry 4). A relatively equal mixture of regioisomers were obtained in the reactions of aryl-alkyl alkynes **2h** and **2i** (Table 3.4, entries 5-6). The cycloaddition of unsymmetrical alkyl-alkyl alkyne **2j** and alkynenitrile **1a** afforded a 1:1 ratio of the pyridine products in a good yield (table 2.4, entry 7). The pyridine product was obtained as a single regioisomer in the reaction of a sterically hindered alkyne **2k** (Table 3.4, entry 8). Interestingly, ^{t}Bu-group is proximal to the nitrogen of the pyridine (entry 8).

The catalytic system is also effective in the intramolecular cycloaddition of dialkynenitriles. Specifically, addition of 20 mol % $Fe(OAc)_2$ and 32 mol % **L12** to substrate **1l** afforded tricyclic product **3v** in 74 % isolated yield (Equation 3.15).

Efforts to isolate an (**L12**)$Fe(OAc)_n$ complex proved unsuccessful. However, the analogous (**L12**)$FeBr_2$ complex[16d] was prepared and used as a catalyst for the

cycloaddition of **1a** and **2a** (Equation 3.16). Importantly, the Fe-ligand complex did catalyze the coupling and afforded pyridine **3a** in 58 % isolated yield. For comparison, reactions run with 10 mol % $FeBr_2$, in lieu of $Fe(OAc)_2$, provided pyridine **3a** in 54 % (GC yield).

Conclusions

We have developed a methodology for the synthesis of pyridines from alkynenitriles and alkynes by employing catalytic amounts of iron acetate and a pyridyl bisimine ligand. This reaction is general for symmetrical and unsymmetrical alkynes. Various groups like alkyl, aryl, trimethylsilyl, and terminal alkynenitriles are reactive in this cycloaddition reaction. Protecting groups like Boc and tosyl are tolerated under the cycloaddition reaction conditions. Alkynenitriles with and without Thorpe-Ingold assistance undergo cycloaddition reactions to afford the pyridine products. Five- and six-Membered bicyclic pyridines can be prepared by this methodology. However, greater than 6-membered tethered bicyclic systems cannot be prepared by this methodology. Exogenous alkynes possessing free hydroxyl or secondary amino groups are not tolerated under these reaction conditions. Efforts to understand the reactivity pattern of the different pyridyl bisimine ligands in the cycloaddition reaction are currently underway. Alkynenitriles **1a** and other coupling partners are also being tested with alkynenitrile using a similar iron catalyst systems in an attempt to discover new reaction methodologies. 2-Aminopyrimidines[17] are structurally important cores and present in various pharmaceutically active compounds. We envisoned a metal catalyzed [2+2+2]

cycloaddition of alkynenitriles and cyanamides (Equation 3.17). Our initial ligand screen has shown that we can synthesize 2-aminopyrimidines in 20 % isolated yield under iron-catalyzed cycloaddition conditions with ligand **L12**. ^{1}H-NMR and gas chromatography-mass spectrometry (GC-MS) data suggests that the 2-aminopyrimidine is formed. Furthur ligand screening and optimization studies are underway.

Experimental

All reactions were conducted under an inert atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove-box unless otherwise noted. Dimethyl formamide (DMF) was purchased from Sigma Aldrich in a sure-seal® bottle. Tetrahydrofuran (THF) was freshly distilled from Na/benzophenone still. Iron acetate (99.995% purity) was purchased from Sigma Aldrich. Alkynenitriles **1a**[18a] **1b**,[18b] **1i**,[19] and **1j**,[20] were prepared by known literature procedures.

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 300 MHz, instruments unless otherwise noted (Inova-400 and Varian VXL-300 spectrometers). All spectra are referenced to residual proteated $CHCl_3$ via a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.26 ppm for ^{13}C. All ^{13}C NMR spectra are proton decoupled. The infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Gas Chromatography was performed on an Agilent 6890 gas chromatography with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 10 ºC/min.; final temperature: 300 ºC

held for 12 min.; detector temperature: 250 ºC. High Resolution Mass Spectroscopy analyses were performed at the University of Utah Mass Spectrometry facility.

Ligands **L1-L6** [23a] and **L7-L10** [23b] were synthesized using reported methods.

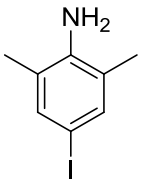
Ligands **L11** and **L12** were synthesized as follows:

Step1 The general procedure was adapted from the literature procedure.[22a] To a stirring mixture of 2,6-substituted aniline and $NaHCO_3$ (3 equiv) in methanol, a solution of iodinemonochloride (1.1 equiv) in CH_2Cl_2 was added dropwise over 1 h (Scheme 3.3, equation 3.18). The reaction was stirred at room temperature for 24 h. Solids were filtered from the mixture and rinsed with diethyl ether. The filtrate was reduced under reduced presure to afford a dark red oil to which a 300 ml solution of saturated sodium thiosulfate was added. The solution was stirred for 10 min then extracted with 3 x 200 mL portions of diethyl ether. The organic extracts were dried with anhydrous Na_2SO_4, filtered, and reduced in vacuo.

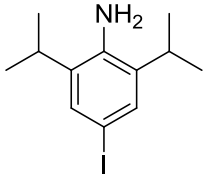
Step 2 The general procedure was adapted from the literature procedure.[22c] In a nitrogen glove box, a 20 ml scintillation vial was filled with CuI (7 mol %) 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4Phen, 14 mol %), Cs_2CO_3 (2.0 equiv), and 4-iodo-2,6-dialkyl aniline (1.0 equiv) (Scheme 3.3, Equation 3.19). The vial was sealed with a rubber septum, removed from the glove box then evacuated and backfilled with Argon three times. Toluene was added and the mixture was stirred at 80 °C for 20 min. Benzyl alcohol (2.0 equiv) was added and the rubber septum was quickly replaced with a vial cap. The reaction was stirred for 24 h at 80 °C then cooled to room temperature, filtered through a silica gel plug, and flushed with 150 ml of ethyl acetate. The resulting solution

was removed under educed pressure and purified using silica gel flash chromatography with 10 % ethyl acetate in hexanes.

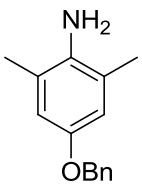
Step 3 The general procedure was adapted from the literature procedure.[22a] 4-benzyloxy-2,6-dialkyl aniline (2.0 equiv.) and 2,6-pyridinedicarboxaldehyde (1.0 equiv) and a catalytic amount glacial acetic acid were stirred in 100 % ethanol overnight at room temperature (Scheme 3.3, Equation 3.20). The mixture was cooled to 0 °C, filtered, and rinsed with cold 100 % ethanol.



Synthesis of 4-iodo-2,6-dimethylaniline: 4-iodo-2,6-dimethylaniline was prepared using the Step 1 general procedure with 2,6-dimethylaniline (10.0 g, 83 mmol), iodinemonochloride (14.7 g, 91 mmol), sodium bicarbonate (20.8 g, 248 mmol). The reaction was stirred at room temperature with 115 ml of methanol and 90 mL of dichloromethane to yield 4-iodo-2,6-dimethylaniline (19.2 g, 93 %) as a dark red oil. Spectral data were compared with known literature value.[24b]

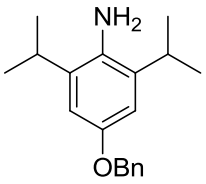


Synthesis of 4-iodo-2,6-diisopropylaniline: 4-iodo-2,6-diisopropyl-aniline was prepared using the Step 1 general procedure with 2,6-diisopropylaniline (10.0 g, 56 mmol), iodinemonochloride (10.1 g, 62 mmol), sodium bicarbonate (14.2 g, 169 mmol). The reaction was stirred at room temperature with 80 ml of methanol and 60 ml of dichloromethane to yield 4-iodo-2,6-diisopropylaniline (16.8 g, 93 %) as a dark red oil. Spectral data were compared with known literature value. [22c]

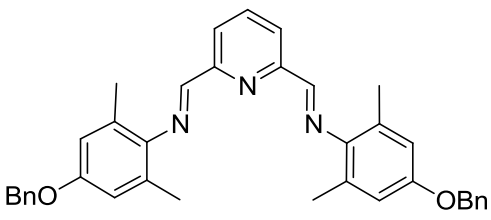


Synthesis of 4-(benzyloxy)-2,6-dimethylaniline: 4-(benzyloxy)-2,6-dimethyl aniline was prepared using the general procedure in Step 2 with

CuI (57.8 mg, 0.30 mmol), Me_4Phen (144 mg, 0.61 mmol), cesium carbonate (1.56 g, 8.1 mmol), 4-iodo-2,6-dimethylaniline (1.0 g, 4.0 mmol), and benzyl alcohol (875 mg, 8.1 mmol). The reaction was run for 24 h at 80 °C in 1.9 ml of toluene to yield 4-(benzyloxy)-2,6-dimethylaniline (363 mg, 40 %) as a blue solid. Mp: 71-73 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.48-7.33 (m, 5H), 6.68 (s, 2H), 5.01 (s, 2H), 3.35 (s, 2H), 2.20 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 151.5, 137.9, 136.9, 128.7, 127.9, 127.7, 123.4, 115.2, 70.9, 18.2. IR (cm^{-1}) 3450, 3375, 3032, 2969, 2908, 2735, 1602, 1489, 1380, 1328, 1298, 1242, 1150, 1054, 856, 738, 698. HRMS (ESI) calcd for $C_{15}H_{17}NO$ $[M+H]^+$ 228.1388, found 228.1385.



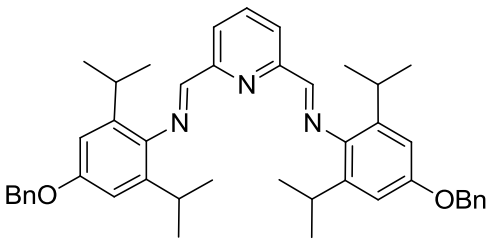
Synthesis of 4-(benzyloxy)-2,6-diisopropylaniline: 4-(benzyloxy)-2,6-diisopropylaniline was prepared using the Step 2 general procedure with CuI (57.8 mg, 0.30 mmol), Me_4Phen (143 mg, 0.61 mmol), cesium carbonate (1.56 g, 8.1 mmol), 4-iodo-2,6-diisopropylaniline (1.0 g, 4.0 mmol), and benzyl alcohol (875 mg, 8.1 mmol). The reaction was run for 24 h at 80 °C in 1.9 ml of toluene to yield 4-(benzyloxy)-2,6-diisopropylaniline (949 mg, 84 %) as a dark red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48-7.27 (m, 5H), 6.74 (s, 2H), 3.48 (s, 2H), 3.01-2.94 (m, 2H), 1.28 (d, J = 6.8 Hz, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 152.4, 138.0, 134.5, 134.4, 128.7, 128.01, 127.96, 110.1, 71.0, 28.4, 22.7. IR (cm^{-1}) 3382, 2960, 1599, 1463, 1347, 1218, 1175, 1100, 1027, 737, 696. HRMS (ESI) calcd for $C_{19}H_{26}NO$ $[M+H]^+$ 284.2014, found 284.2013.



L11

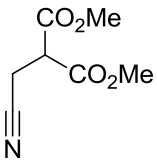
Synthesis of (*N*,*N*'E,*N*,*N*'E)-*N*,*N*'-(pyridine-2,6-diylbis(methanylylidene))bis(4-(benzyloxy)-2,6-

dimethylaniline) (**L11**): Compound **L11** was pre- pared using the Step 3 general procedure with 4-(benzyloxy)-2,6-dimethylaniline (195 mg, 0.86 mmol), 2,6-pyridinedicarboxaldehyde (57.8 mg, 0.43 mmol), and 5 drops of glacial acetic acid. The reaction was run at room temperature in 10 ml of 100 % ethanol yielding **L11** (108 mg, 46 %) as a yellow solid. Mp: 174-177 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40 (s, 2H), 8.38 (d, *J* = 8.0 Hz, 2H), 7.97 (t, *J* = 7.8 Hz, 1H), 7.47-7.33 (m, 10H), 7.76 (s, 4H), 5.06 (s, 4H), 2.20 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm). IR (cm^{-1}) 3087, 2970, 2948, 1602, 1584, 1480, 1455, 1379, 1332, 1312, 1198, 1052, 738, 698. HRMS (ESI) calcd. for $C_{37}H_{35}N_3O_2$ $[M+H]^+$ 576.2627, found 576.2633.

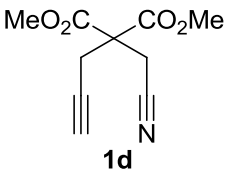


L12

Synthesis of (*N*,*N*'E,*N*,*N*'E)-*N*,*N*'-(pyridine-2,6-diylbis(methanylylidene))bis(4-(benzyloxy)-2,6-diisopropylaniline) (**L12**): Compound **L12** was prepared using the Step 3 general procedure with 4-(benzyloxy)-2,6-diisopropylaniline (2.35 g, 8.3 mmol), 2,6-pyridinedicarboxaldehyde (600 mg, 4.1 mmol), and 10 drops of glacial acetic acid. The reaction was run at room temperature in 10 ml of 100 % ethanol to yield **L12** (2.48 g, 85%) as a yellow solid. M.p. 170-173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.40-8.38 (m, 4H), 7.99 (t, *J* = 8.0 Hz, 1H), 7.51-7.28 (m, 10H), 6.83 (s, 4H), 5.08 (s, 4H), 3.07-2.98 (m, 4H), 1.18 (d, *J* = 7.2 Hz, 24H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 163.4, 156.3, 154.8, 142.4, 139.1, 137.6, 137.5, 128.1, 128.2, 128.0, 122.8, 109.9, 70.5, 28.4, 23.7. IR (cm^{-1}) 3391, 2961, 2869, 1637, 1600, 1458, 1326, 1190, 1026, 736. HRMS (ESI) calcd. for $C_{45}H_{51}N_3O_2$ $[M+H]^+$ 688.3879, found 688.3882.



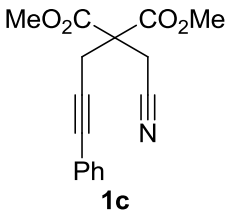
Synthesis of dimethyl-2-(cyanomethyl)malonate: To a stirring suspension of NaH (1.8 g, 75.7 mmol) in 150 ml THF was added dimethylmalonate (10 g, 75.7 mmol) (Equation 3.21) under N_2 counter-flow. The resulting solution was stirred at room temperature for 1 h after which time bromoacetonitrile (5.0 g, 42.1 mmol) was added. The mixture was stirred at room temperature for 24 h at which time the solution was quenched with 100 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organic layers were washed with brine (100 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude yellow oil was purified by flash column chromatography (20 % EtOAc/hexanes) to yield dimethyl-2-(cyanomethyl) malonate (4.1 g, 57 %) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 3.78 (s, 6H), 3.73 (t, *J* = 7.2 Hz, 1H), 2.89 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167, 116.8, 53.5, 47.8, 17.1



1d

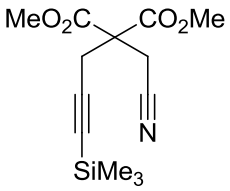
Synthesis of dimethyl 2-(cyanomethyl)-2-(prop-2-yn-1-yl)malonate (**1d**): Dimethyl-2-(prop-2-yn-1-yl)malonate was prepared by known literature procedure.[23] To a stirring suspension of NaH (0.21 g, 8.82 mmol) in 50 ml THF was added dimethyl-2-(prop-2-yn-1-yl)malonate (1.0 g, 5.88 mmol) (Equation 3.22) under N_2 counter-flow. The resulting solution was stirred at room temperature for 1 h after which time bromoacetonitrile (1.0 g, 8.82 mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux for 8-12 h at which time GC analysis showed no starting material. The solution was cooled to room temperature and quenched with 100 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 100 ml). The combined

organics were washed with brine (100 ml), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The resulting crude yellow oil was purified by flash column chromatography (10 % EtOAc/hexanes then 12 % EtOAc/ hexanes) to yield **1d** (0.6 g, 49 %) as pale yellow oil. ^1H (400 MHz, $CDCl_3$): 3.83 (s, 6H), 3.17 (s, 2H), 3.03 (d, J = 2.8 Hz, 2H), 2.13 (t, J = 2.8 Hz, 1H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 168.3, 116.4, 81.0, 71.8, 53.9, 24.2, 22.1, 3.7. IR (cm^{-1}) 3288, 2960, 2253, 1743, 1483, 1327, 1217, 971, 892. HRMS calculated for $C_{10}H_{11}NO_4Na$ 232.0586, found 232.0592.



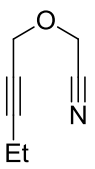
1c

Synthesis of dimethyl-2-(cyanomethyl)-2-(3-phenylprop-2-yn-1-yl)malonate (**1c**): $Pd(PPh_3)_2Cl_2$ (28.4 mg, 0.04 mmol) and CuI (27.7 mg, 0.14 mmol) were added to a solution of **1d** (3.0 g, 14.5 mmol) in Et_3N (17 ml) (Equation 3.23). To the mixture was added a solution of phenyl iodide (1.6 g, 8.1 mmol). The resulting mixture was stirred at 50 °C for 6 h. The reaction was quenched by the addition of water and extracted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl, and the water layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on a silica gel column chromatography (10 % EtOAc/hexanes) which furnished **1c** (1.2 g, 52 % yield) as a dark brownish yellow oil. ^1H (400 MHz, $CDCl_3$): δ (ppm) 7.34 (m, 5H), 3.85 (s, 6H), 3.25 (s, 2H) 3.22 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.1, 132.0, 128.7, 128.5, 122.6, 116.2, 85.2, 82.3, 55.5, 54.0, 24.7, 22.3. IR (cm^{-1}) 2957, 2253, 1743, 1438, 1295, 1215, 1030. HRMS (ESI) calculated for $C_{16}H_{15}NO_4Na$ $(M+Na)^+$ 308.0899, observed 308.0895.



1e

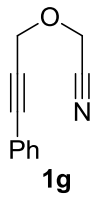
Synthesis of dimethyl 2-(cyanomethyl)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)malonate (**1e**): To a stirring suspension of NaH (0.12 g, 4.82 mmol) in 30 ml THF was added dimethyl-2-(cyanomethyl)malonate (0.55 mg, 3.21 mmol) under N_2 (Equation 3.24). The resulting solution was stirred at room temperature for 1 h after which time (3-bromoprop-1-yn-1-yl)trimethylsilane (0.50 g, 4.82 mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux for 12 h at which time GC analysis showed no starting material. The solution was cooled to room temperature and quenched with 70 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 70 ml). The combined organics were washed with brine (100 ml), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting crude yellow oil was purified by flash column chromatography (20 % EtOAc/hexanes) to yield **1e** (0.79 g, 87 %) as a colorless solid. Mp: 34-36 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 6H), 3.14 (s, 2H), 3.03 (s, 2H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 116.2, 99.1, 90.5, 55.4, 53.9, 25.4, 22.1, 0.1. IR (cm^{-1}): 2960, 2902, 2253, 2181, 1746, 1437, 1322, 1294, 1028, 847. HRMS calculated for $C_{13}H_{19}NO_4NaSi$ 304.0981, found 304.0977.



1f

Synthesis of 2-(pent-2-yn-1-yloxy)acetonitrile (**1f**): To a stirring suspension of NaH (0.7 g, 30.9 mmol) in 25 ml THF was added pent-2-yn-1-ol (2.0 g, 23.8 mmol) (Equation 3.25) under N_2 counter-flow in two portions. The resulting solution was stirred at room temperature for 1 h after which time bromoacetonitrile (3.7 g, 30.9 mmol) was added. The reaction mixture was stirred at room temperature for 8-12 h at which time GC analysis showed no starting material. The solution was cooled and

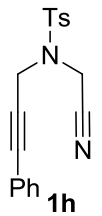
quenched with 100 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organics were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude yellow oil was purified by flash column chromatography (10 % EtOAc/hexanes) to yield **1f** (1.2 g, 42 %) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.34 (s, 2H), 4.28 (t, *J* = 4.4 Hz, 2H), 2.25 (m, 2H), 1.15 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 115.9, 91.3, 72.8, 58.9, 54.0, 13.7, 12.5. IR (cm^{-1}) 2980, 2919, 2292, 1452, 1320, 1140, 1092, 902. HRMS (ESI) calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$ 124.0762, found 124.0776.



1g

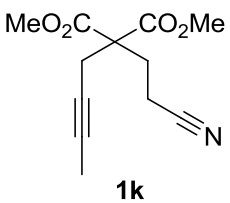
Synthesis of 2-((3-phenylprop-2-yn-1-yl)oxy)acetonitrile (**1g**): To a stirring suspension of NaH (0.3 g, 9.1 mmol) in 50 ml THF was added 3-phenylprop-2-yn-1-ol (2.0 g, 7.57 mmol) under N_2 counter-flow (Equation 3.26). The resulting solution was stirred at room temperature for 1 h after which time bromoacetonitrile (1.1 g, 9.1 mmol) was added. The mixture was stirred at room temperature for 12 h at which time GC analysis showed no starting material. The solution was cooled and quenched with 100 mL of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organics were washed with brine (100 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude yellow oil was purified by silica gel flash column chromatography (20 % EtOAc/hexanes) to yield **1g** (1.2 g, 92 %) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (m, 2H), 7.36 (m, 3H), 4.55 (s, 2H), 4.43 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.0, 129.2, 128.6,

121.9, 115.9, 88.8, 82.3, 59.1, 54.3. IR cm^{-1} 3060, 2908, 2857, 2242, 1964, 172.0762, found 172.0728.



1h

Synthesis of *N*-(cyanomethyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzene sulfonamide (**1h**): To a stirring suspension of NaH (0.05 g, 1.9 mmol) in 20 ml THF was added 4-methyl-*N*-(3-phenylprop-2-yn-1yl)benzenesulfonamide[24] (0.5 g, 1.7 mmol) under N_2 (Equation 3.27). The resulting solution was stirred at room temperature for 1 h after which time bromoacetonitrile (0.2 g, 1.9 mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux for 12 h at which time GC analysis showed no starting material. The solution was cooled to room temperature and quenched with 100 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organics were washed with brine (100 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude yellow oil was purified by flash column chromatography (30 % EtOAc/hexanes) to yield **1h** (0.34 g, 60 %) as a colorless solid. Mp: 97-99 °C. ^1H (400 MHz, $CDCl_3$): δ (ppm) 7.78 (d, *J* = 8Hz, 2H), 4.28 (t, *J* = 4.4 Hz, 2H), 2.25 (m, 2H), 1.15 (t, *J* = 7.6 Hz, 3H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 145.2, 134.3, 131.9, 130.3, 129.2, 128.5, 128.1, 121.8, 113.8, 87.6, 80.1, 38.8, 35.4, 21.8. IR (cm^{-1}) 2958, 2253, 1744, 1438, 1215, 1072, 759. HRMS (ESI) calculated for $C_{18}H_{16}N_2O_2NaS$ (M+Na) 347.0830, observed: 347.0835.

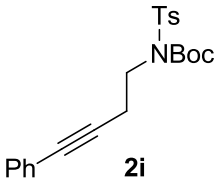


1k

Synthesis of dimethyl-2-(but-2-yn-1-yl)-2-(2-cyanoethyl)malonate (**1k**): To a stirring suspension of NaH (0.24 g, 10.1 mmol) in 100 ml THF was added dimethyl malonate (2.0 g, 15.1 mmol) under N_2 (scheme 3.4). The resulting solution was stirred at room temperature for 1 h after which

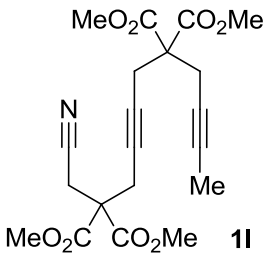
time bromopropionitrile (1.35 g, 10.1 mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux for 12 h at which time the solution was cooled to room temperature and quenched with 100 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 100 ml). The combined organics were washed with brine (100 ml), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The resulting crude yellow oil was purified by silica gel flash column chromatography (40 % EtOAc/hexanes) to yield dimethyl-2-(2-cyanoethyl)malonate (1.2 g, 64 %) as a pale yellow oil. Spectral data were compared with known literature values.[25]

To a stirring suspension of NaH (0.16 g, 6.5 mmol) in 50 ml THF was added dimethyl-2-(2-cyanoethyl)malonate (1g, 5.4 mmol) under N_2. The resulting solution was stirred at room temperature for 1 h after which time 1-bromo-2-butyne (0.86 g, 6.5 mmol) was added. A reflux condenser was attached and the mixture was stirred at reflux for 12 h at which time the solution was cooled to room temperature and quenched with 50 ml of a saturated NH_4Cl solution. The layers were separated and aqueous layer was extracted with Et_2O (3 x 50 ml). The combined organics were washed with brine (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude yellow oil was purified by silica gel flash column chromatography (40 % EtOAc/hexanes) to yield **1k** (0.6 g, 50 %) as a colorless solid. Mp: 62-63 °C. ^1H (400 MHz, $CDCl_3$): δ (ppm) 3.78 (s, 6H), 2.79 (q, J = 2.4 Hz, 2H), 2.44 (m, 4H), 1.77 (t, J = 2.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.0, 119.2, 80.3, 72.4, 56.2, 53.3, 28.9, 24.2, 13.2, 3.7. IR (cm^{-1}) 2957, 2249, 1736, 1441, 1340, 1209. HRMS $C_{12}H_{15}NO_4Na$ calculated 260.0899, observed 260.0898.



2i

Synthesis of tert-butyl(4-phenylbut-3-yn-1-yl)tosylcarbamate (**2i**): Under N_2, diisopropylazodicarboxylate (1.7 ml, 8.92 mmol, 1.1 equiv) was added to a solution of *N*-(*tert*-butyoxycarbonyl)-*p*-toluene sulfonamide (2.2 g, 8.1 mmol, 1 equiv), triphenylphosphine (8.9 g, 1.3 mmol, 1.1 equiv) and 4-phenylbut-3-yn-1-ol [26] (1.3 g, 8.92 mmol, 1.1 equiv) in a dropwise fashion at 0 °C (Equation 3.28). The reaction mixture was then stirred at room temperature for 15 h. The solvent was removed under reduced pressure. Hexanes (100 ml) were added to the resultant yellow mixture and the white precipitate was filtered. The solid was pre-absorbed on silica gel and purified by flash column chromatography (20 % EtOAc and Hexanes) affording the product **2i** as a white solid (3.1 g, 96 %). Mp: 98-99 °C. ^{1}H (400 MHz, $CDCl_3$) δ (ppm) 7.84 (d, *J*= 6.8 Hz, 2H), 7.38 (m, 2H), 7.28 (m, 5H), 4.10 (t, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 8 Hz, 2H), 2.43 (s, 3H), 1.35 (s, 9H). ^{13}C (100 MHz, $CDCl_3$) δ ppm 151.1, 144.4, 137.6, 131.9, 129.5, 128.4, 128.2, 128.1, 123.7, 86.3, 84.7, 82.8, 45.6, 28.1, 21.8, 21.1. IR (in cm^{-1}): 3058, 2980, 2932, 1739, 1598, 1357, 1287, 1162, 970, 846, 693. HRMS (ESI) calculated for m/z $C_{22}H_{25}NO_4NaS$ $(M+Na)^+$ 422.1402, observed 422.1403.



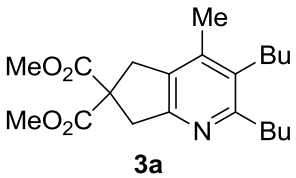
1l

Synthesis of tetramethyl-1-cyanoundeca-4,9-diyne-2,2,7,7-tetra carboxylate (**1l**): Dimethyl-2-(4-bromobut-2-yn-1-yl)-2-(but-2-yn-1-yl)malonate [27] was then added to a solution of NaH (92 mg, 3.85 mmol), THF (40 ml), and dimethyl-2-(cyanomethyl) malonate (0.6 g, 3.5 mmol) which was previously stirred at room temperature for 1 h (Equation 3.30). After the addition was complete the reaction mixture was refluxed for 12-15 h. The completion of the reaction was monitored by gas chromatography. The

reaction was later quenched by addition of 50 ml saturated ammonium chloride and distilled water 20 ml and extracted with diethyl ether (3x 100 ml). All organic layers were washed with brine and then dried over magnesium sulfate. The organic layers were concentrated under reduced pressure to afford a crude oil. The crude oil was then purified by silica gel column chromatography using silica gel to afford **1l** (1.2 g, 86 %) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.81 (s, 6H), 3.75 (s, 6H), 3.12 (s, 2H), 2.98 (t, *J* = 2 Hz, 2H), 2.93 (t, *J* = 2.4 Hz, 2H), 2.84 (q, *J* = 2.4 Hz, 2H), 1.75 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.6, 168.1, 116.3, 79.7, 79.5, 723.0, 56.9, 55.3, 53.9, 53.2, 24.1, 23.2, 23.1, 22.0, 3.7. IR (cm^{-1}): 2958, 2848, 2251, 1741, 1437, 1294, 1214, 1056, 952, 819.

General Procedure for Cycloaddition

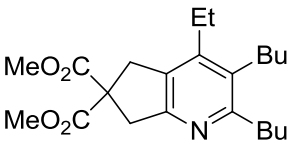
In a nitrogen filled glove box, a solution of alkynenitrile (>1.0 M in DMF) was added to a vial containing 10 mol % $Fe(OAc)_2$ and 13 mol % **L12**. Additional DMF was added to make the final concentration of alkynenitrile 0.4 M (accounting for alkyne volume). The mixture was stirred for 10 min then 1 equiv. of alkyne and 20 mol % of zinc dust was added. The vial was capped and removed from the glove box then stirred at 85 °C for the indicated period of time. The crude mixture was purified via silica gel flash chromatography.



3a

Synthesis of dimethyl-2,3-dibutyl-4-methyl-5H-cyclopenta [b]pyridine-6,6(7H)-dicarboxylate (**3a**): Compound **3a** was prepared using the general procedure with **1a** (51.3 mg, 0.23

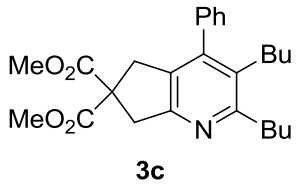
mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 2 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3a** (58.2 mg, 70 %) as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.75 (s, 6H), 3.70 (s, 2H), 3.64 (s, 2H), 2.72 (t, *J* = 8 Hz, 2H), 2.56 (t, *J* = 8 Hz, 2H), 2.19 (s, 3H), 1.62 (m, 2H), 1.42 (m, 2H), 0.93 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.4, 159.8, 156.6, 141.6, 123.3, 130.3, 57.7, 53.2, 42.2, 38.1, 35.6, 33.0, 32.5, 28.4, 23.4, 23.3, 15.9, 14.2, 14.1. IR (cm^{-1}) 3476, 2963, 2019, 1736, 1582, 1438, 1380, 1241, 1071, 963, 863, 818, 737. HRMS (ESI) calcd for $C_{21}H_{32}NO_4$ $[M+H]^+$ 362.2331, found 362.2338.



3b

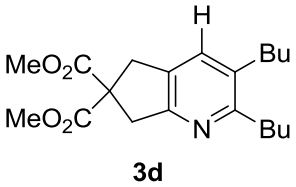
Synthesis of dimethyl-2,3-dibutyl-4-ethyl-5H-cyclopenta[b] pyridine-6,6(7H)-dicarboxylate (**3b**): Compound **3b** was prepared using the general procedure with **1a** (81.8 mg, 0.23 mmol), **2a** (47.7 mg, 0.35 mmol), $Fe(OAc)_2$ (6.0 mg, 3.5 x 10^{-2} mmol), **L12** (29.9 mg, 4.5 x 10^{-2} mmol), and zinc (4.5 mg, 6.9 x 10^{-2} mmol) in 800 µL of dimethylformamide. The reaction was stirred at 85 °C for 4 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3b** (103 mg, 86 %) as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.75 (s, 6H), 3.63 (s, 2H), 3.51 (s, 2H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.62 (q, *J* = 7.2 Hz, 2H), 2.20 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H), 1.10 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.3, 160.4, 157.1, 147.4, 131.4, 129.7, 58.1, 53.2, 42.0, 37.5, 42.0, 37.5, 35.5, 33.7, 33.0, 27.9, 23.5, 23.4, 23.3, 14.2, 14.04, 13.98. IR (cm^{-1}) 3476, 2958, 1744, 1580, 1437,

1408, 1378, 1253, 1104, 1070, 964, 905, 865, 736. HRMS (ESI) calcd for $C_{22}H_{34}NO_4$ $[M+H]^+$ 376.2488, found 376.2497.



3c

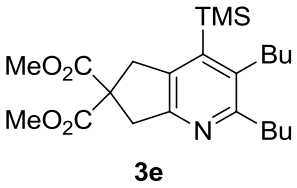
Synthesis of dimethyl-2,3-dibutyl-4-phenyl-5H-cyclopenta[b] pyridine-6,6(7H)-dicarboxylate (**3c**): Compound **3c** was prepa red using the general procedure with **1c** (98.4 mg, 0.35 mmol), **2a** (47.7 mg, 0.35 mmol), $Fe(OAc)_2$ (6.0 mg, 3.5 x 10^{-2} mmol), **L12** (29.9 mg, 4.5 x 10^{-2} mmol), and zinc (4.5 mg, 6.9 x 10^{-2} mmol) in 800 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 4 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3c** (137 mg, 75 %) as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (t, *J* = 8 Hz, 2H), 7.36 (d, *J* = 7.2, 1H), 7.17 (d, *J* = 8 Hz, 2H), 3.71 (s, 6H), 3.22 (s, 2H), 2.78 (t, *J* = 10 Hz, 2H), 2.41 (t, *J* = 8 Hz, 2H), 1.70 (q, *J* = 7.2 Hz, 2H), 1.46 (sext, *J* = 7.2 Hz, 2H), 1.28 (q, *J* = 6.8 Hz, 2H), 1.15 (q, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.2, 3H), 0.71 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1, 160.6, 156.9, 146.8, 138.2, 131.6, 129.7, 128.6, 128.2, 127.7, 57.9, 42.3, 38.4, 35.4, 33.2, 32.9, 28.6, 23.3, 22.9, 14.2, 13.7. IR (cm^{-1}) 2956, 2869, 1783, 1576, 1490, 1437, 1273, 1198, 1073, 964, 739. HRMS (ESI) calcd for $C_{26}H_{34}NO_4$ $[M+H]^+$ 424.2488, found 424.2484.



3d

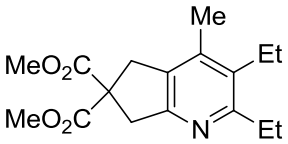
Synthesis of dimethyl 2,3-dibutyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3d**): Compound **3d** was prepared using the general procedure with **1d** (32.8 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction was stirred at 85 °C for 26 h and the resulting brown mixture was purified with silica gel flash

chromatography using 10 % ethyl acetate in hexanes to yield **3d** (24.0 mg, 30 %) as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 (s, 1H), 3.76 (s, 6H), 3.65 (s, 2H), 3.54, (s, 2H), 2.76 (t, *J* = 8 Hz, 2H), 2.56 (t, *J* = 8 Hz, 2H), 1.63 (m, 4H), 1.53 (m, 4H), 1.42 (m, 4H), 0.95 (td, *J* = 7.2 Hz, 1.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.2, 159.7, 157.7, 133.8, 133.2, 130.6, 58.4, 53.3, 41.9, 38.5, 35.0, 33.4, 32.6, 32.2, 30.6, 23.3, 22.9, 14.24, 14.17. IR (cm^{-1}) 3286, 2958, 2868, 1737, 1603, 1572, 1437, 1379, 1249, 1072, 969, 853, 654. HRMS (ESI) calcd for $C_{26}H_{34}NO_4$ $[M+H]^+$ 348.2175, found 348.2176.



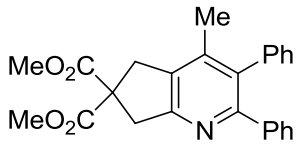
3e

Synthesis of dimethyl 2,3-dibutyl-4-(trimethylsilyl)-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3e**): Compound **3e** was prepared using the general procedure with **1e** (64.7 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 26 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3e** (55.0 mg, 57 %) as a viscous, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.75 (s, 6H), 3.60 (s, 4H), 2.72 (t, *J* = 8 Hz, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.64 (m, 4H), 1.42 (m, 4H), 0.96 (m, 6H), 0.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.3, 159.3, 156.5, 144.4, 138.8, 136.0, 58.3, 53.2, 41.3, 41.0, 35.4, 35.3, 33.0, 32.2, 29.9, 23.4, 23.3, 14.2, 14.1, 2.4. IR (cm^{-1}) 3476, 2957, 2870, 2179, 1739, 1556, 1436, 1376, 1253, 1200, 1167, 1072, 1049, 965, 877, 843, 762, 695, 633. HRMS (ESI) calcd for $C_{23}H_{38}NO_4$ $[M+H]^+$ 420.2570, found 420.2579.



3f

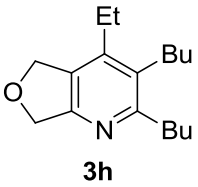
Synthesis of dimethyl 2,3-diethyl-4-methyl-5H-cyclopenta[b] pyridine-6,6(7H)-dicarboxylate (**3f**): Compound **3f** was prepared using the general procedure with **1a** (100.0 mg, 0.45 mmol), **2b** (36.8 mg, 0.45 mmol), $Fe(OAc)_2$ (7.8 mg, 4.5 x 10^{-2} mmol), **L12** (38.8 mg, 5.8 x 10^{-2} mmol), and zinc (5.9 mg, 9.0 x 10^{-2} mmol) in 1.0 mL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 6 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3f** (97.0 mg, 71%) as a viscous, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.77 (s, 6H), 3.65 (s, 2H), 3.52 (s, 2H), 2.78 (q, *J* = 7.8 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.21 (s, 3H), 1.29-1.23 (m, 3H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.3, 160.6. 156.7, 141.6, 133.4, 130.5, 57.7, 53.2, 42.2, 38.1, 28.7, 21.6, 15.6, 14.9, 14.5. IR (cm^{-1}) 2965, 1737, 1584, 1437, 1377, 1259, 1071, 961, 928, 864, 820, 733. HRMS (ESI) calcd for $C_{17}H_{24}NO_4$ $[M+H]^+$ 306.1705, found 306.1707.



3g

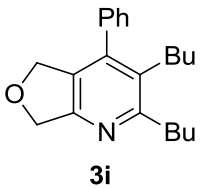
Synthesis of dimethyl-4-methyl-2,3-diphenyl-5H-cyclopenta [b]pyridine-6,6(7H)-dicarboxylate (**3g**): Compound **3g** was prepared using the general procedure with **1a** (100.0 mg, 0.45 mmol), **2c** (159.7 mg, 0.90 mmol), $Fe(OAc)_2$ (7.8 mg, 4.5 x 10^{-2} mmol), **L12** (38.8 mg, 5.8 x 10^{-2} mmol), and zinc (5.9 mg, 9.0 x 10^{-2} mmol) in 1.1 mL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 6 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3g** (88.0 mg, 54 %) as a viscous, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.27-7.02 (m, 10H), 3.82 (s, 8H), 3.65 (s, 2H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm). IR (cm^{-1}) 3057, 2854, 1737, 1601, 1554, 1495, 1432,

1400, 1266, 1201, 1121, 1073, 908, 862, 819, 797, 771, 736, 701, 574. HRMS (ESI) calcd for $C_{25}H_{24}NO_4$ $[M+H]^+$ 402.1705, found 402.1700.



3h

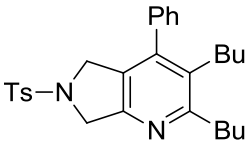
Synthesis of 2,3-dibutyl-4-ethyl-5,7-dihydrofuro[3,4-b]pyridine (**3h**): Compound **3h** was prepared using the general procedure with **1f** (28.3 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 26 h and the resulting brown mixture was purified with silica gel flash chromatography using 10% ethyl acetate in hexanes to yield **3h** (25 mg, 41 %) as a yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.13 (s, 2H), 5.02 (s, 2H), 2.77, (t, *J* = 8.4 Hz, 2H), 2.64-2.50 (m, 4H), 1.71-1.6 (m, 2H), 1.50-1.41 (m, 6H), 1.15 (t, *J* = 7.8 Hz, 3H), 1.00-0.93 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 160.9, 156.9, 145.2, 131.6, 128.7, 73.4, 71.9, 35.4, 33.7, 32.8, 27.6, 23.7, 23.4, 23.2, 14.1, 14.02, 13.97. IR (cm^{-1}) 2959, 1768, 1583, 1462, 1406, 1376, 1304, 1186, 1104, 1049, 903, 795, 742. HRMS (ESI) calcd for $C_{17}H_{28}NO$ $[M+H]^+$ 262.2171, found 262.2173.



3i

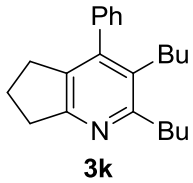
Synthesis of 2,3-dibutyl-4-phenyl-5,7-dihydrofuro[3,4-b]pyridine (**3i**): Compound **3i** was prepared using the general procedure with **1g** (39.4 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 4 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3i** (37.8 mg, 45 %) as a colorless solid. M.p. 49-50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 (m, 3H), 7.19 (m, 2H), 5.1 (s, 2H), 4.8 (s,

2H), 2.85 (t, *J* = 8.0 Hz, 2H), 2.49 (t, *J* = 8.0 Hz, 2H), 1.74 (m, 2H), 1.45 (sext, *J* = 7.2 Hz, 2H), 1.34 (m, 2H), 1.18 (sext, *J* = 7.2 Hz, 2H), 0.98 (t, *J* = 7.6 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.3, 156.9, 144.5, 137.9, 131.9, 129.0, 128.8, 128.1, 128.0, 73.8, 72.6, 35.5, 33.4, 32.9, 28.4, 23.3, 23.0, 14.2, 13.7. IR (cm^{-1}) 3058, 2957, 1952, 1780, 1581, 1497, 1463, 1399, 1289, 1257, 1181, 1101, 1042, 999, 900, 849, 748, 704, 647. HRMS (ESI) calcd for $C_{21}H_{28}NO$ $[M+H]^+$ 310.2171, found 310.2171.



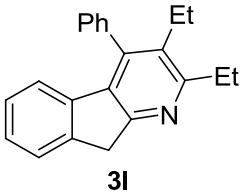
3j

Synthesis of 2,3-dibutyl-4-phenyl-6-tosyl-6,7-dihydro-5H-pyrrolo [3,4-b]pyridine (**3j**): Compound **3j** was prepared using the general procedure with **1h** (74.6 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 4 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3j** (43.5 mg, 41 %) as a colorless solid (M.P. 158-160 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.71 (d, *J* = 8Hz, 2H), 7.43 (q, *J* = 6.0, 7.2, 8.0 Hz, 4H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.10 (dd, *J* = 18.4, 0.8 Hz, 2H), 4.63 (s, 2H), 4.28 (s, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.41 (t, *J*= 5.6 Hz, 5H), 1.68 (q, *J*= 7.6 Hz, 2H), 1.43 (sext, *J*= 7.6 Hz, 2H), 1.26 (q, *J* = 7.2 Hz, 2H), 0.96 (t, *J* = 7.2, 3H), 0.71 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.8, 153.3, 145.7, 143.9, 137.2, 134.0, 132.7, 130.0, 129.0, 128.3, 127.9, 127.8, 126.7, 54.5, 52.4, 35.4, 33.2, 32.7, 28.5, 23.2, 23.0, 21.7, 14.2, 13.7. IR (cm^{-1}) 3064, 2957, 2926, 2860, 1725, 1494, 1212, 1097, 1061, 966, 740. HRMS (ESI) calcd for $C_{28}H_{35}N_2O_2$ $[M+H]^+$ 463.2419, found 463.2426.



3k

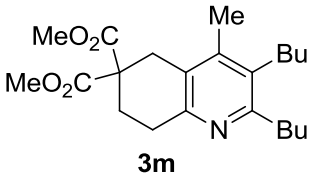
Synthesis of 2,3-dibutyl-4-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (**3k**): Compound **3k** was prepared using the general procedure with **1i** (38.9 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 4 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3i** (54.3 mg, 65 %) as a yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.46-7.39 (m, 3H), 7.19 (dd, *J* = 1.5 Hz, 6.6 Hz, 2H), 5.09 (s, 2H), 4.84 (s, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.49 (t, *J* = 7.5 Hz, 2H), 1.79 (m, 2H), 1.48 (sext, *J* = 7.5 Hz, 2H), 1.38-1.12 (m, 6H), 0.98 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 161.6, 159.1, 146.7, 139.0, 133.2, 130.3, 128.5, 128.32, 128.25, 127.3, 35.5, 34.7, 33.3, 33.1, 30.4, 28.6, 23.3, 23.0, 22.9, 14.2, 13.6. IR (cm^{-1}) 3057, 3029, 2959, 1950, 1725, 1573, 1496, 1462, 1393, 1338, 1243, 1178, 1104, 1073, 1028, 964, 916, 846, 739, 703, 619. HRMS (ESI) calcd for $C_{22}H_{30}N$ $[M+H]^+$ 308.2378, found 308.2384.



3l

Preparation of 2,3-diethyl-4-phenyl-9H-indeno[2,1-b]pyridine (**3l**): Compound **3l** was prepared using the general procedure with **1j** (50.0 mg, 0.23 mmol), **2b** (18.9 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 552 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 2 h. The resulting brown mixture was loaded onto a silica gel plug and flushed with 100 ml of ethyl acetate which was concentrated to afford brownish colored oil. The brown oil was dissolved in 5 ml of dichloromethane and 5 ml of acetone and

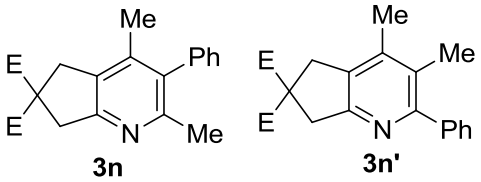
stirred with 10 ml of 6 M HCl for 2 h. The aqueous layer was extracted with 3 x 25 ml portions of dichloromethane and the organic layer was collected and concentrated. The resulting greenish-yellow oil was dissolved in minimal dichloromethane and loaded onto a silica plug. The silica plug was then washed with 100 ml of ethyl acetate and the resulting filtrate was discarded. A 100 ml solution of 1 % acetic acid in ethyl acetate was passed through the plug which was also discarded. Then 200 ml of 30 % acetic acid in ethyl acetate was run through the plug, collected and concentrated under reduced pressure. The brown oil was stirred with 5 ml of diethyl ether, 5 ml of dichloromethane and 10 mL of saturated $NaHCO_3$ for 10 min. The biphasic mixture was extracted with 3 x 20 ml portions of diethyl ether. The organic extracts were concentrated under reduced pressure to yield **3l** (44.2 mg, 64 %) as a crystalline yellow solid. Mp: 118-122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56-7.50 (m, 4H), 7.31 (d, *J* = 2.0 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.15 (d, *J* = 8.0 Hz, 1H), 3.99 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 161.4, 159.9, 144.5, 141.8, 140.2, 138.4, 132.9, 131.1, 129.2, 128.6, 128.1, 126.7, 125.1, 122.7, 38.7, 28.8, 22.2, 15.8, 15.0. IR (cm^{-1}). HRMS (ESI) calcd for $C_{22}H_{22}N$ $[M+H]^+$ 300.1752, found 300.1746.



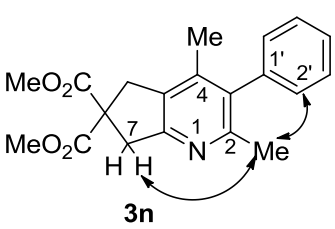
3m

Synthesis of dimethyl 2,3-dibutyl-4-methyl-7,8-dihydroquinoline-6,6(5H)-dicarboxylate (**3m**): Compound **3m** was prepared using the general procedure with **1k** (54.6 mg, 0.23 mmol), **2a** (32.8 mg, 0.23 mmol), $Fe(OAc)_2$ (4.0 mg, 2.3 x 10^{-2} mmol), **L12** (20 mg, 3.1 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 533 µL of *N*,*N*-dimethylformamide. The reaction mixture was stirred at 85 °C for 24 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield

3m (34.5 mg, 40%) as yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.74 (s, 6H), 3.12 (s, 2H), 2.86 (t, *J*= 6.5 Hz, 2H), 2.70 (t, *J*= 8.5, 2H), 2.59 (t, *J*= 8 Hz, 2H), 2.37 (t, *J*= 7.0 Hz, 2H), 2.19 (s, 3H), 1.62 (m, 2H), 1.44 (m, 6H), 0.96 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.8, 157.4, 150.4, 131.6, 127.7, 124.8, 53.7, 52.8, 35.5, 32.6, 32.3, 32.0, 29.5, 28.5, 27.7, 23.3, 23.1, 14.6, 14.0, 13.8. IR (cm^{-1}) 2957, 2870, 1738, 1665, 1571, 1438, 1332, 1242, 1169, 1084, 1027, 976, 858, 792, 737, 700. HRMS (ESI) calcd for $C_{22}H_{34}NO_4$ $[M+H]^+$ 376.2488, found 376.2486.

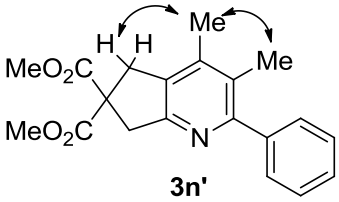


Dimethyl-2,4-dimethyl-3-phenyl-5H- cyclopenta [b]pyridine-6,6(7H)-dicarboxylate (**3n**) and dimethyl-3,4-dimethyl-2-phenyl-5H-cyclopenta [b]pyridine-6,6-(7H)-dicarb- oxylate (**3n'**): Compounds **3n** and **3n'** were prepared using the general procedure with **1a** (100 mg, 0.45 mmol) and **2e** (52 mg, 0.45 mmol), 10 mol % $Fe(OAc)_2$ (7.80 mg, 4.5 x10^{-2} mmol), 13 mol% of **L12** (39.7 mg, 5.9 x10^{-2} mmol), and zinc (5.9 mg, 9.0 x 10^{-2} mmol) in *N*,*N*-dimethylformamide. After 6 h the crude reaction mixture was purified by silica gel flash column chromatography using 100 ml hexanes then 20 % ethyl acetate in hexanes to afford 3m and 3m' in a 1.2:1.0::**3n**:**3n'** as yellowish oils (105.3 mg, 69 % yield).



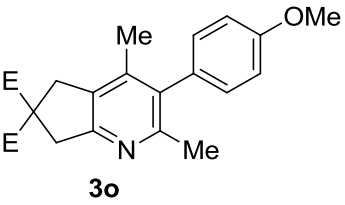
3n: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (d, *J* = 8.4 Hz, 2H), 7.34 (m, 1H), 7.41 (m, 2H), 3.78 (s, 6H), 3.71 (s, 2H), 3.55 (s, 2H), 2.21 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 158.2, 155.5, 141.7, 139.1, 135.5, 130.1, 129.3, 128.8, 127.4, 127.4, 57.8, 53.3, 42.2, 37.8, 23.7, 17.1. IR (cm^{-1}) 3472, 2954, 1737, 1575, 1437, 1273, 1071, 868, 705. nOe correlation of a) the methyl

group on C-2 and the phenyl ring and b) between the methyl on C-2 and the methylene on the C-7 of the 5-membered ring. HRMS (ESI) calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$ 340.1549, found 340.1552.

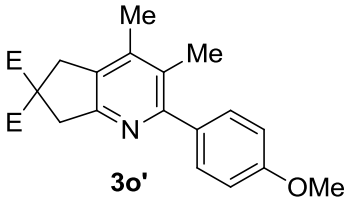


3n'

3n': ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (d, *J* = 4 Hz, 4H), 7.36 (t, *J* = 4.4 Hz, 1H), 3.78 (s, 6H), 3.72 (s, 2H), 3.6 (s, 2H), 2.25 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 158.4, 157.1, 142.8, 141.5, 131.3, 129.3, 128.3, 127.9, 127.7, 57.9, 53.3, 42.2, 37.9, 16.5, 16.4. IR (cm^{-1}) 3055, 2955, 1736, 1575, 1436, 1269, 1073, 738, 703. nOe correlation between the 2 methyl groups and the methyl group with the methylene on the 5-membered ring. HRMS (ESI) calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$ 340.1549, found 340.1553.

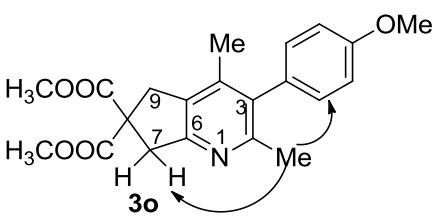


3o



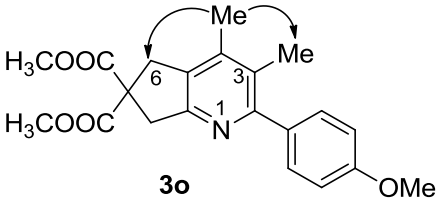
3o'

<u>Synthesis of dimethyl-3-(4-methoxyphenyl)-2,4dimethyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3o**) and dimethyl-2-(4-methoxyphenyl)-3,4-dimethyl-5H-cyclopenta-[b]pyridine-6,6(7H)-dicarboxylate (**3o'**) :</u> Compounds **3o** and **3o'** were prepared using the general procedure with **1a** (100 mg, 0.45 mmol) and **2f** (65 mg, 0.45 mmol), 10 mol % $Fe(OAc)_2$ (7.80 mg, $4.5x10^{-2}$ mmoles), 13 mol % of **L12** (39.7 mg, 5.9 $x10^{-2}$ mmol), and zinc (5.9 mg, 9.0 x 10^{-2} mmol) in *N*,*N*-dimethylformamide. After 6 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes then 20 % ethyl acetate in hexanes and finally 30 % ethyl acetate and hexanes to afford **3o** and **3o'** in a 3:2::**3o**:**3o'** as oils (65.2 mg, 39 % yield).



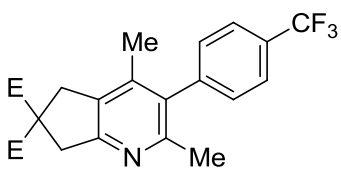
3o

3o: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.02 (d, *J*= 8.8Hz, 2H), 6.96 (d, *J*= 8.4Hz 2H), 7.41 (m, 2H), 3.86 (s, 3H), 3.79 (s, 6H), 3.72 (s, 2H), 3.55 (s, 2H), 2.23 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 158.9, 158.0, 156.0, 142.3, 135.1, 131.2, 130.5, 130.2, 114.3, 57.9, 55.5, 53.3, 42.2, 37.9, 23.8, 17.2. IR (cm^{-1}): 3053, 2956, 2842, 1736, 1515, 1269, 1246, 1071, 838, 737. nOe correlation between 1) the methyl group on C-2 and methylene protons on C-7 and 2) the methyl group on C-2 and the phenyl ring protons. HRMS (ESI) calcd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$ 370.1654, found 370.1660.

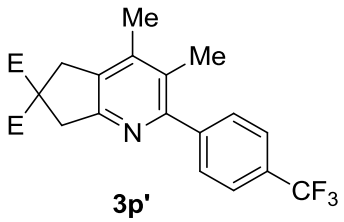


3o

3o': ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.37 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.78 (s, 6H), 3.71 (s, 2H), 3.59 (s, 2H), 2.25 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 159.3, 158.1, 157.1, 142.8, 134.2, 130.9, 130.6, 127.9, 113.8, 58.0, 55.5, 53.3, 42.2, 38.0, 16.6, 16.5. IR (cm^{-1}): 2955, 2840, 1736, 1608, 1437, 1247, 1107, 1071, 839, 765. nOe correlation between a) the methyl group on C-4 and the methylene on C-6 of the 5-membered ring and b) the methyl group on C-4 and the methyl group on C-3. HRMS (ESI) calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$ 370.1654, found 370.1660.



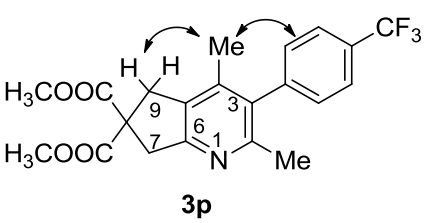
3p



3p'

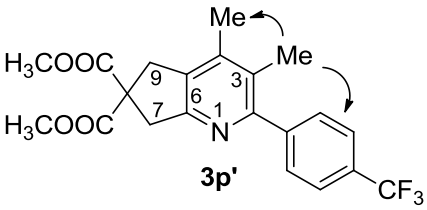
Synthesis of dimethyl-2,4-dimethyl-3-(4-(trifluoromethyl) phenyl)-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3p**) and dimethyl-3,4-dimethyl-2-(4-(trifluoromethyl)phenyl)-5H-cyclopenta[b]pyridine-

6,6(7H)-dicarboxylate (**3p'**): Compounds **3p** and **3p'** were prepared using the general procedure with **1a** (100 mg, 0.45 mmol) and **2g** (65 mg, 0.45 mmol), 10 mol % $Fe(OAc)_2$ (7.80 mg, $4.5x10^{-2}$ mmol), 13 mol % of **L12** (39.7 mg, 5.9 $x10^{-2}$ mmol), and zinc (5.9 mg, 9.0 x 10^{-2} mmol) in DMF. After 4 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes then 20 % ethyl acetate in hexanes, and finally 30 % ethyl acetate in hexanes to afford **3p** and **3p'** in a 4:1::**3p**:**3p'** as yellowish oils (63.7 mg, 39 %).



3p

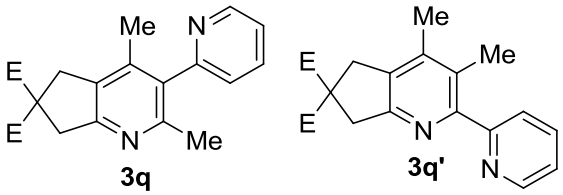
3p: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.02 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 7.41 (m, 2H), 3.86 (s, 3H), 3.79 (s, 6H), 3.72 (s, 2H), 3.55 (s, 2H), 2.23 (s, 3H), 1.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 159, 155.2, 143.1, 141.4, 134.0, 130.3, 130.0, 129.9, 125.9 (q, *J* = 15.2 Hz), 125.7, 57.7, 53.3, 42.2, 37.9, 23.8, 17.2. IR (cm^{-1}): 2956, 2927, 2856, 1737, 1615, 1438, 1325, 1167, 1126, 1067, 848. nOe correlation between a) the methyl on C-4 and the methylene on C-6 and b) the methyl group on C-4 and the phenyl ring protons. HRMS (ESI) calcd for $C_{21}H_{21}NO_4F_3$ $[M+H]^+$ 408.1423, found 408.1425.



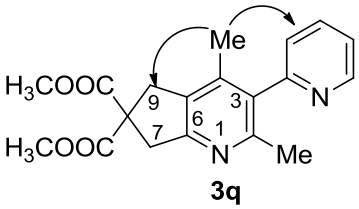
3p'

3p': ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69 (d, *J* = 8 Hz, 2H), 7.25 (d, *J* = 8 Hz, 2H), 3.78 (s, 6H), 3.71 (s, 2H), 3.55 (s, 2H), 2.19 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 159.0, 155.2, 143.1, 141.5, 134.0, 131.8, 130.3, 130.0, 126.0 (q, *J* = 15.2 Hz), 128.8, 125.9, 57.8, 53.4, 42.3, 37.8, 23.8, 17.1. nOe correlation between a) the methyl group on C-3

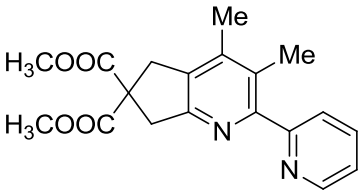
and the phenyl and b) between the methyl group on C-3 and C-4. HRMS (ESI) calculated for $C_{19}H_{21}N_2O_4$ $[M+H]^+$ 370.16, found 370.1660.



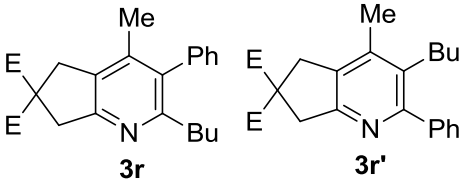
Synthesis of dimethyl-2,4-dimethyl-3-(pyridine-2-yl)-5H-cyclopenta[b]pyridine-6,6-(7H)-dicarboxylate (**3q**) and dimethyl-3,4-dimethyl-2-(pyridin-2-yl)-5H-cyclopenta[b] pyridine-6,6(7H)-dicarboxylate(**3q'**): Compounds **3q** and **3q'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2g** (39.4 mg, 0.22 mmol) with 10 mol % $Fe(OAc)_2$ (3.89 mg, 2.2 x 10^{-2} mmol), 13 mol % of **L12** (19.83 mg, 2.9 x 10^{-2} mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in DMF. After 5 h the crude reaction mixture was purified via flash column chromatography using using 50 % EtOAc in hexanes then 2 % dichloromethane in methanol, and finally 5 % dichloromethane in methanol to afford **3q** and **3q'** in a 7:3::**3q**:**3q'** as yellowish oils (42.7 mg, 56 %).



3q: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.80 (s, 1H), 7.70 (dt, *J*= 8 Hz, 1.2 Hz, 1H), 7.28 (m, 1H), 7.21 (d, *J*= 7.6 Hz, 1H), 3.77 (s, 6H), 3.70 (s, 2H), 3.54 (s, 2H), 2.22 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 159.2, 158.3, 155.4, 150.1, 141.7, 136.8, 134.2, 130.3, 124.9, 122.4, 58.0, 53.3, 42.2, 37.7, 23.3, 16.7. IR (cm^{-1}): 2954, 2924, 2851, 1736, 1588, 1434, 1274, 1071, 964, 823. nOe correlation between a) the methyl group on C-4 and the pyridyl ring protons and b) methyl group on C-4 and the methylene protons on C-9 of the 5-membered ring. HRMS (ESI) calcd for $C_{19}H_{21}N_2O_4$ $[M+H]^+$ 341.1517, found 341.1511.

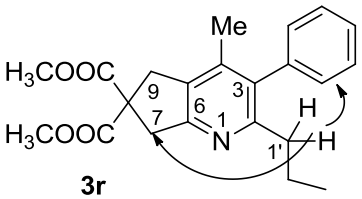


3q': ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.70 (s, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.28 (m, 1H), 3.78 (s, 6H), 3.73 (s, 2H), 3.61 (s, 2H), 2.26 (d, *J*= 4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.2, 159.8, 157.3, 156.4, 149.0, 143.4, 136.7, 132.4, 129.0, 124.6, 122.6, 58.1, 53.4, 42.2, 38.0, 16.5, 15.9. IR (cm^{-1}): 2954, 2924, 2853, 1736, 1585, 1436, 1276, 1072, 964. HRMS (ESI) calculated for $C_{19}H_{21}N_2O_4$ $[M+H]^+$ 341.1501, found 341.1505



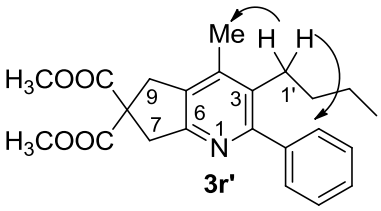
<u>Synthesis of dimethyl-2-butyl-4-methyl-3-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3r**) and dimethyl-3-butyl-4-methyl-2-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3r'**):</u>

Compounds **3r** and **3r'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2i** (26.2 mg, 0.22 mmol), 10 mol % $Fe(OAc)_2$ (3.89 mg, $2.2x10^{-2}$ mmol), 13 mol % of **L12** (19.8 mg, 2.9 $x10^{-2}$ mmol), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in DMF. After 16 h the crude was isolated and was purified via silica gel flash column chromatography using 100 ml hexanes and then 20 % EtOAc in hexanes to afford **3q** and **3q'** in a 3:2::**3r**:**3r'** as oils (45.2 mg, 53 %).

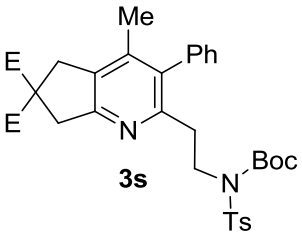


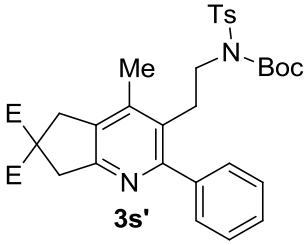
3r: ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.36 (m, 5H), 3.76 (s, 6H), 3.71 (s, 2H), 3.60 (s, 2H), 2.53 (t, *J* = 8.4 Hz, 2H), 2.29 (s, 3H), 1.35 (s, 2H), 1.21 (sext, *J* = 7.2 Hz, 2H), 0.77 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 159.0, 156.8, 142.3, 141.8, 132.9, 131.8, 128.9, 128.2, 127.6, 57.8, 53.3, 42.2, 38.1, 32.5, 29.0, 23.0, 16.0, 13.8. IR (cm^{-1}): 2956, 2860, 1737, 1574, 1437, 1273, 1071, 736, 705. nOe correlation

between a) the methylene protons on C-1' and the aryl ring protons and b) methylene group on C-1' and the methylene protons on C-7 of the 5-membered ring. HRMS (ESI) calcd for $C_{23}H_{27}NO_4$ $[M+H]^+$ 382.2018, found 382.2022.



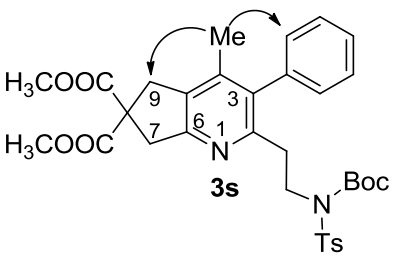
3r': ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (m, 3H), 7.60 (td, *J* = 6.8 Hz, 1.6 Hz, 2H) 3.80 (s, 6H), 3.74 (s, 2H), 3.56 (s, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.91 (s, 3H), 1.76 (sext, *J* = 7.6 Hz, 2H), 0.73 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 159.7, 158.4, 141.9, 139.0, 135.0, 129.9, 129.0, 128.6, 127.4, 57.7, 53.3, 42.4, 38.0, 36.1, 32.6, 22.9, 17.2, 14.0. IR (cm^{-1}): 2956, 2870, 1737, 1436, 1274, 1071, 961, 862, 735, 702. nOe correlation between a) the methylene protons on C-1' and the aryl ring protons and b) methylene protons on C-1' and the methyl protons on C-4. HRMS (ESI) calcd for $C_{23}H_{28}NO_4$ $[M+H]^+$ 382.2018, found 382.2032.



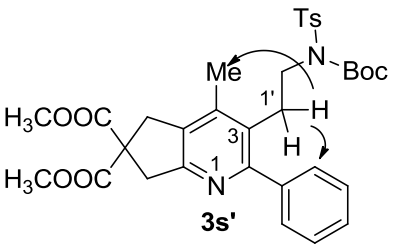


<u>Synthesis of dimethyl-2-(2-(N-(tert) butoxycarbonyl)-4-methylphenylsulfo-namide)ethyl)-4-methyl-3-phenyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarbo xylate (**3s**) and dimethyl 3-[2-(*N*-(tert-butoxycarbonyl)-4-(methylphenylsulfonamido)ethyl)]-4-methyl-2-phenyl-5H-cyclopenta [b]pyridine-6,6-(7H)-dicarboxylate (**3s'**)</u>: Compounds **3s** and **3s'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol), **2i** (26.2 mg, 0.22 mmol), 10 mol % $Fe(OAc)_2$ (3.89 mg, 2.2 $x10^{-2}$ mmol), 13 mol % of **L12** (19.8 mg, 2.9 $x10^{-2}$ mmol) catalyst, and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in DMF. After 16 h the crude reaction mixture was purified via silica gel flash column chromatography using 100 ml hexanes,

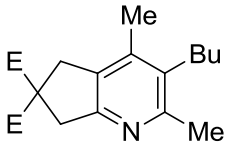
then 20 % EtOAc in hexanes and finally 40% EtOAc in hexanes to afford **3s** and **3s'** in a 3:2::**3s**:**3s'** as yellowish oils (61.8 mg, 44 %).



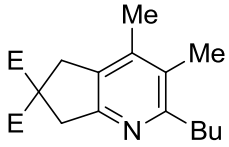
3s: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.52 (d, *J* = 8.4 Hz, 2H), 7.44 (m, 4H), 7.39 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 3.80 (s, 6H), 3.74 (s, 2H), 3.61 (s, 2H), 3.03 (t, *J* = 8.4 Hz, 2H), 2.42 (d, *J* = 8.4 Hz, 6H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.2, 160.0, 158.0, 151.0, 144.3, 143.6, 141.3, 137.5, 132.1, 129.4, 129.1, 128.6, 128.2, 128.1, 127.9, 84.6, 57.8, 53.4, 46.1, 42.3, 38.1, 30.1, 28.1, 21.8, 16.3. nOe correlation between a) the methyl group at C-4 and the protons of phenyl ring and b) the methyl group on C-4 and the methylene protons on C-9 of the 5-membered ring. IR (cm^{-1}): 2956, 1734, 1575, 1437, 1400, 1278, 1159, 1090, 969, 736. HRMS (ESI) calcd. for $C_{33}H_{38}N_2O_8SNa$ $[M+Na]^+$ 645.2247, found 645.2264.



3s': ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61(d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 7.2 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 4.12 (t, *J* = 7.6 Hz, 2H), 3.80 (s, 6H), 3.72 (s, 2H), 3.57 (s, 2H), 2.86 (t, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 1.92 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 158.7, 155.6, 151.0, 144.0, 141.7, 138.5, 137.7, 135.6, 130.4, 129.6, 129.2, 128.9, 128.1, 127.5, 84.0, 57.8, 53.3, 46.8, 42.2, 37.9, 35.8, 28.0, 21.8, 17.2. nOe correlation between a) the methylene on C1' and the protons on the phenyl ring and b) the methylene on C1' and the protons on the methyl group. IR (cm^{-1}): 2956, 1734, 1596, 1439, 1400, 1277, 1159, 1088, 970, 735. HRMS (ESI) calcd for $C_{33}H_{38}N_2O_8SNa$ $[M+Na]^+$ 645.2247, found 645.2254.

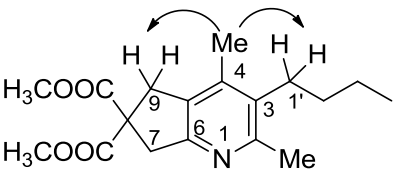


3t



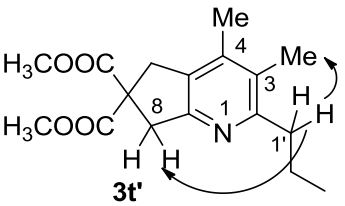
3t'

Synthesis of dimethyl-3-butyl-2,4-dimethyl-5H-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3t** and dimethyl-2-butyl-3,4-dimethyl-5H-cyclopen ta[b]pyridine-6,6(7H)-dicarboxylate (**3t'**): Compounds **3t** and **3t'** were prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2j** (28.9 mg, 0.22 mmol), 10 mol % $Fe(OAc)_2$ (3.89 mg, 2.2 x10^{-2} mmol) and 13 mol% of **L12** (19.83 mg, 2.9 x10^{-2} mmol) catalyst, and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 0.53 ml DMF. After 16 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes, then 20 % EtOAc in hexanes and finally 30 % EtOAc in hexanes to afford **3t** and **3t'** in a 1:1::**3t**:**3t'** as oils (44.3 mg, 62 %).



3t

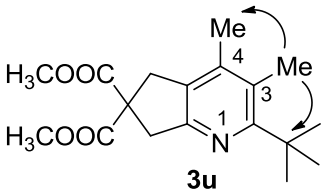
3t: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.76 (s, 3H), 3.63 (s, 2H), 3.51 (s, 2H), 2.57 (t, *J* = 8 Hz, 2H), 2.50 (s, 3H), 2.20 (s, 3H), 1.42 (m, 4H), 0.96 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.3, 156.4, 155.7, 141.4, 133.0, 130.6, 57.9, 53.3, 42.2, 38.1, 31.6, 28.9, 23.3, 22.8, 15.8, 14.1. IR (cm^{-1}) 2956, 2869, 1737, 1586, 1437, 1274, 1070, 961, 736. nOe correlation between a) the methyl group on C-4 and the methylene protons on C-1' and b) methyl group on C-4 and the methylene protons on C-9 of the 5-membered ring. HRMS (ESI) calcd. for $C_{18}H_{26}NO_4$ $[M+H]^+$ 320.1862, found 320.1867.



3t'

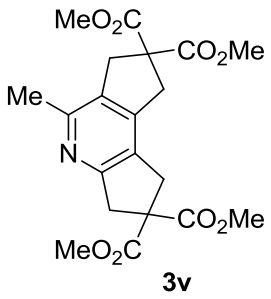
3t': ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.76 (s, 6H), 3.65 (s, 2H), 3.52 (s, 2H), 2.76 (t, *J* = 8.4 Hz, 2H), 2.17 (d, *J* = 3.6 Hz, 6H), 1.60 (m, 2H), 1.43 (sext, *J* = 7.6 Hz, 2H), 0.94

(t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.3, 159.8, 156.5, 142.0, 130.1, 127.6, 57.9, 53.3, 42.2, 38.0, 36.5, 32.0, 23.2, 16.5, 14.5, 14.2. IR (cm^{-1}) 2956, 1737, 1583, 1436, 1378, 1273, 1199, 1163, 1103, 1071, 962, 863, 735. nOe correlation between a) the methylene of the butyl group on C-2 and the methylene group on C-8 and b) the methylene on C-2 and methyl on C-3. HRMS (ESI) calcd for $C_{18}H_{25}NO_4$ $[M+H]^+$ 320.1862, found 320.1866.



3u

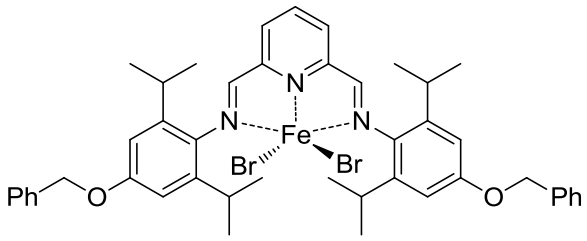
Synthesis of dimethyl-2-(tert-butyl)-3,4-dimethyl-(5H)-cyclopenta[b]pyridine-6,6(7H)-dicarboxylate (**3u**): Compound **3u** was prepared using the general procedure with **1a** (50 mg, 0.22 mmol) and **2j** (28.9 mg, 0.22 mmol), 10 mol % $Fe(OAc)_2$ (3.89 mg, 2.2 $x10^2$mmoles), 13 mol % of **L12** (19.8 mg, 2.9 $x10^{-2}$ mmoles), and zinc (3.0 mg, 4.6 x 10^{-2} mmol) in 0.53 ml DMF. After 16 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes, then 20 % EtOAc in hexanes and finally 30 % EtOAc in hexanes to afford **3u** as a single product as an oil (44.3 mg, 26 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.78 (s, 6H), 3.66 (s, 2H), 3.53 (s, 2H), 2.35 (s, 2H), 2.16 (s, 3H), 1.43 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.5, 165.0, 155.2, 142.9, 129.7, 128.7, 128.0, 57.7, 53.2, 42.4, 38.8, 38.1, 30.6, 24.4, 23.7, 22.7, 17.1, 16.7. IR (cm^{-1}): 2956, 2900, 1731, 1638, 1438, 1273, 1199, 1071, 961, 737, 701. nOe correlation between a) the methyl group on C-3 and another methyl group on C-4 and b) between the methyl on C-3 and the *t*-butyl group on C-2. HRMS (ESI) calcd for $C_{18}H_{26}NO_4$ $[M+H]^+$ 320.1862, found 320.1861.



3v

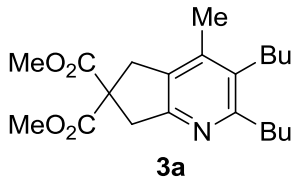
Synthesis of tetramethyl-5-methyl-dicyclopenta[b,d]-pyridine-2,2,7,7(1H,3H,6H,8H)-tetracarboxylate (**3v**):The general procedure was used with **1i** (50 mg, 0.12 mmol) with 20 mol % $Fe(OAc)_2$ (4.3 mg, 3.2 $x10^{-2}$ mmoles) and 32 mol % of **L12** (21.4 mg, 2.5 $x10^{-2}$ mmoles), and zinc dust (3.2 mg, 4.9 $x10^{-2}$) in 0.4 ml DMF. After 24 h the crude reaction mixture was purified via flash column chromatography using 100 ml hexanes, then 30 % EtOAc in hexanes and finally 50 % EtOAc in hexanes to afford **3v** as yellowish oil (37 mg, 74 %).

3v: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.76 (s, 6H), 3.75 (s, 6H), 3.62 (s, 2H), 3.52 (s, 2H), 3.49 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 172.1, 171.9, 159.3, 152.9, 145.5, 132.7, 126.8, 59.8, 58.3, 53.4, 41.8, 39.4, 39.1, 37.1, 22.0. IR (cm^{-1}): 2955, 2850, 1736, 1592, 1434, 1266, 1200, 1068, 961, 860, 737. HRMS (ESI) calcd for $C_{20}H_{24}NO_4$ $[M+H]^+$ 406.1502, found 406.1502



Synthesis of $FeBr_2$ and L12 complex**:** The $FeBr_2$-**L12** complex was prepared by a previous reported method[28] using $FeBr_2$ (20 mg, 9.2 $x10^{-2}$ mmol), **L12** (61.8 mg, 9.2 $x10^{-2}$ mmol) in THF in the glove box. The reaction mixture was stirred for 3 h and then filtered over celite. Removal of THF under reduced pressure afforded the complex as a dark green solid. ^{1}H NMR (300 MHz, CD_2Cl_2) (All peaks appeared broad) δ (ppm) 59.5 (2H), 14.02 (4H), 7.55 (17H), 0.34 (28H), 3.62 (s, 2H), 3.52 (s, 2H), 3.49 (s, 2H), 2.42 (s, 3H). Crystals were grown by slow diffusion of diethyl ether from dichloromethane. Based on the preliminary crystal structure analysis, we found that the

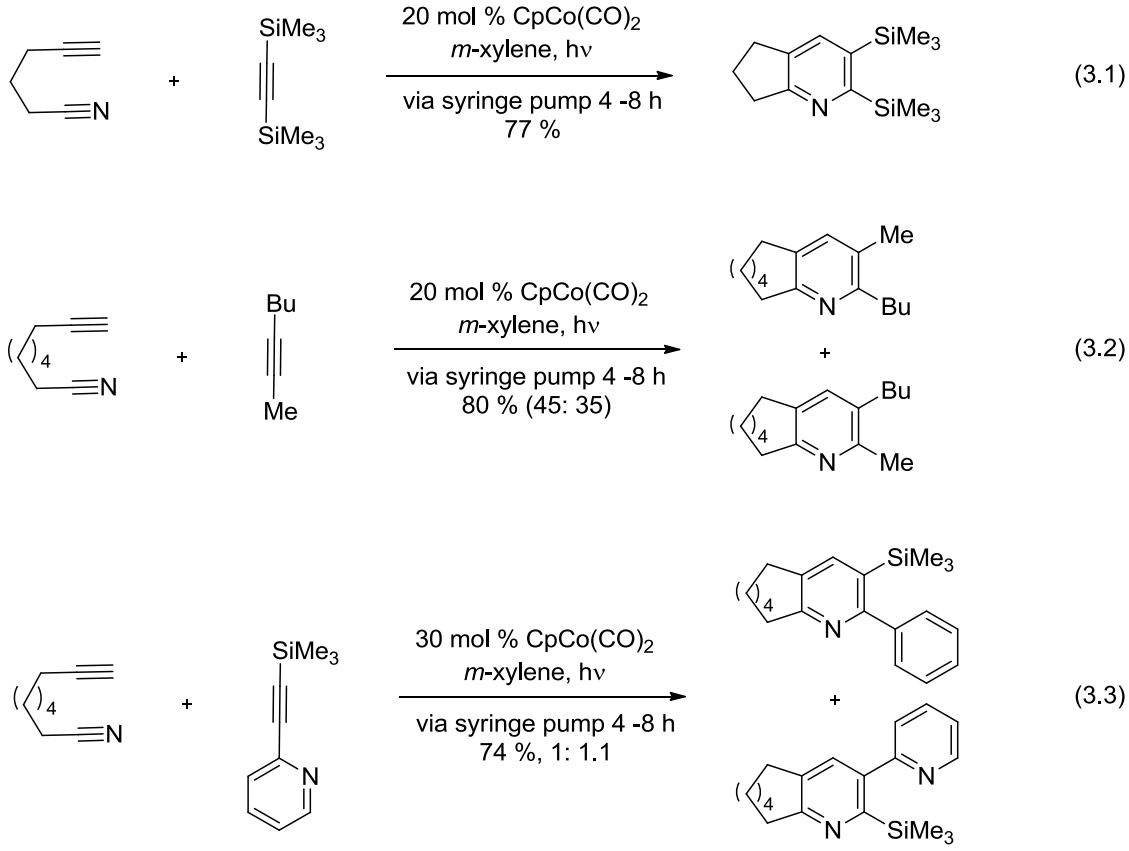
iron is coordinated to the 3 nitrogens of **L12**. The crystal system is triclinic A= 8.8401 Å, B= 9.9680 Å, C= 27.2923 Å, α = 90.91°, β = 94.59°, γ = 113.99°. Unit cell volume = 2194.98 Å, Space group = Pī. Disorder in the *p*-substituted benzyloxy region was also observed.

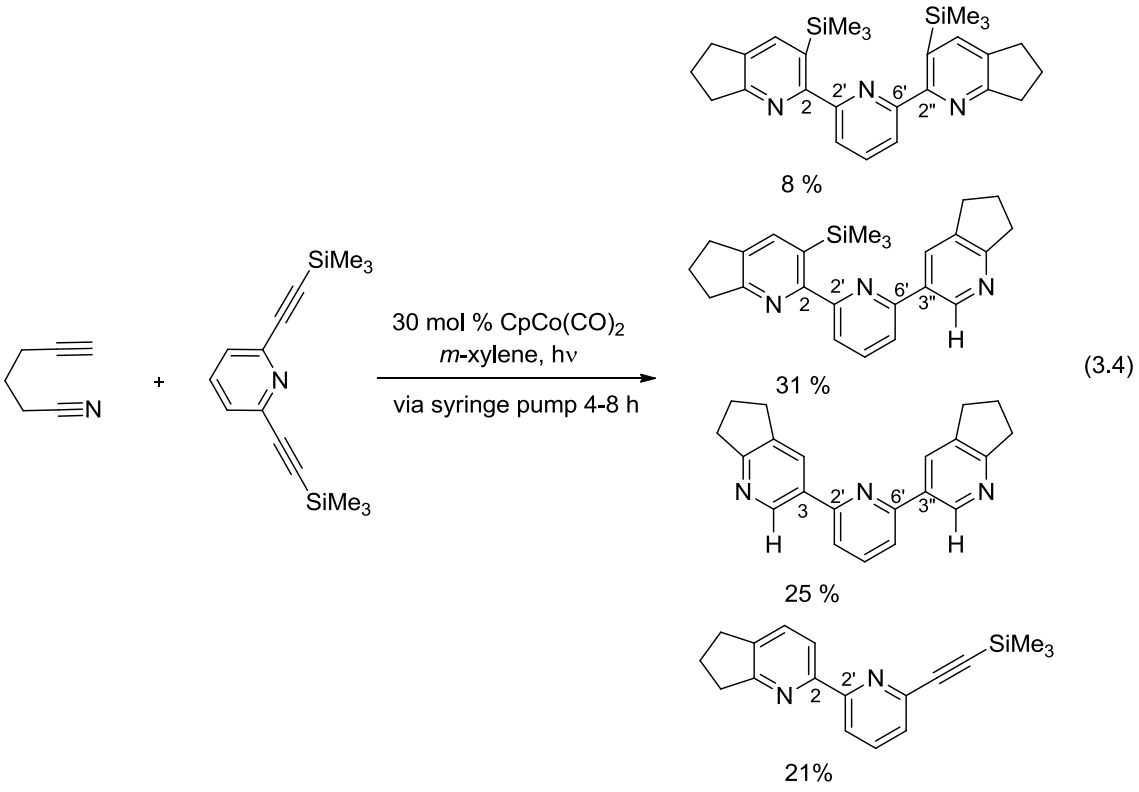


3a

Compound **3a** was prepared using **1a** (51.3 mg**,** 0.23 mmol) **2a** (32.8 mg, 0.23 mmol), $FeBr_2$-L12 complex (20.3 mg, 2.3x 10^{-2} mmol), and zinc (30 mg, 4.6x10^{-2} mmol) in 533µL of *N*,*N*-dimethyl formamide. The reaction mixture was stirred at 85 °C for 2 h and the resulting brown mixture was purified with silica gel flash chromatography using 10 % EtOAc in hexanes to yield **3a** (48 mg, 58 %) as a viscous yellow oil (reported above).

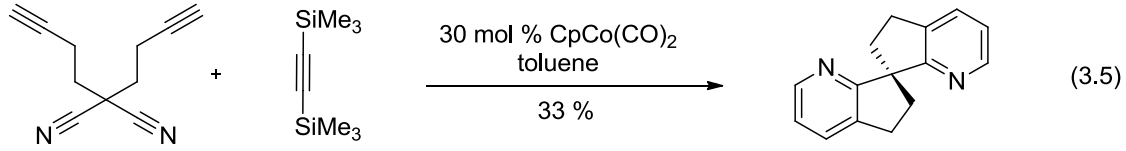
Scheme 3.1 Co-catalyzed reactions of alkynenitriles and alkyne (Equations 3.1-3.3)



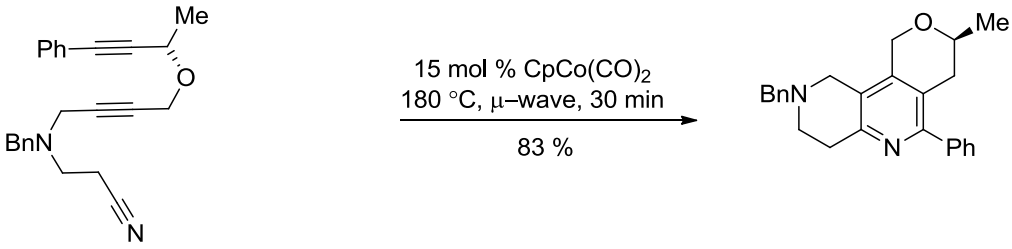

SiMe3
SiMe3
N
2
2'
N
6'
2"
N
8 %
SiMe3
2'
N
6'
3"
N
N
2
H
31 %
N
3
H
2'
N
6'
3"
N
H
25 %
SiMe3
2'
N
N
2
21%
+
N
SiMe3
SiMe3
30 mol % CpCo(CO)2
m-xylene, hν
via syringe pump 4-8 h

(3.4)

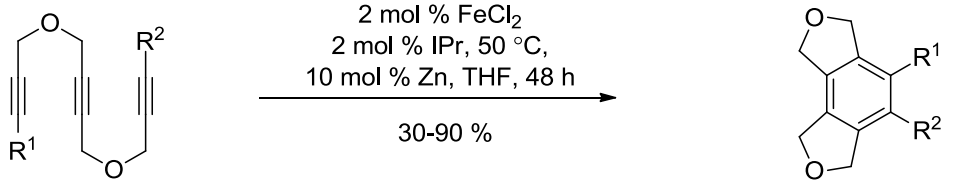
Scheme 3.2 *Spiro*-pyridines and a tricyclic pyridine synthesis (Equation 3.5 and 3.6)



(3.5)

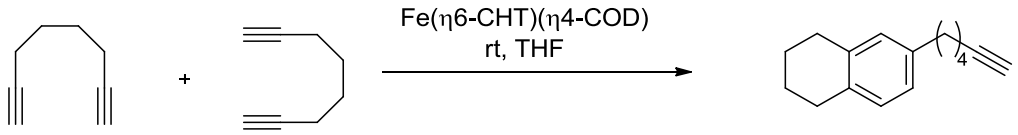


(3.6)

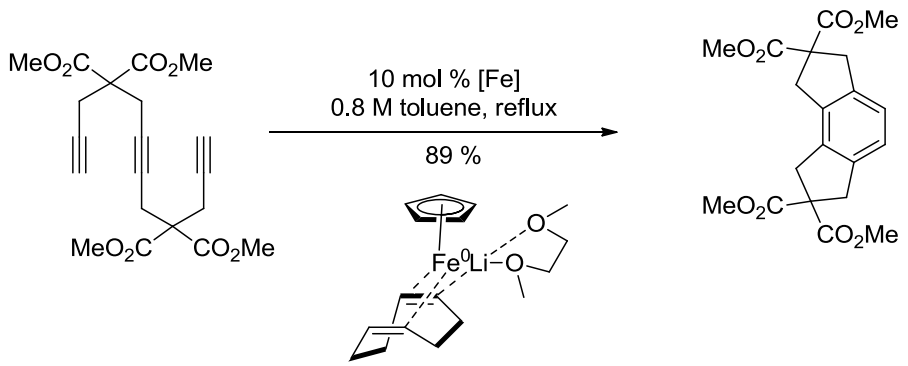


(3.7)

$R^1 = R^2 = H$
$R^1 = R^2 = {}^n Bu$
$R^1 = R^2 = SiMe_3$



(3.8)



(3.9)

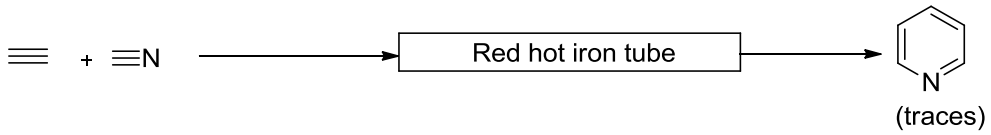
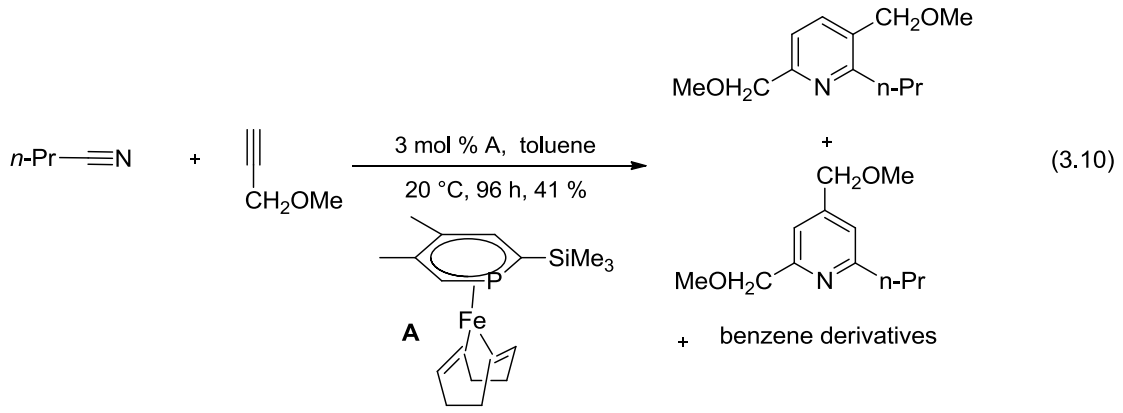
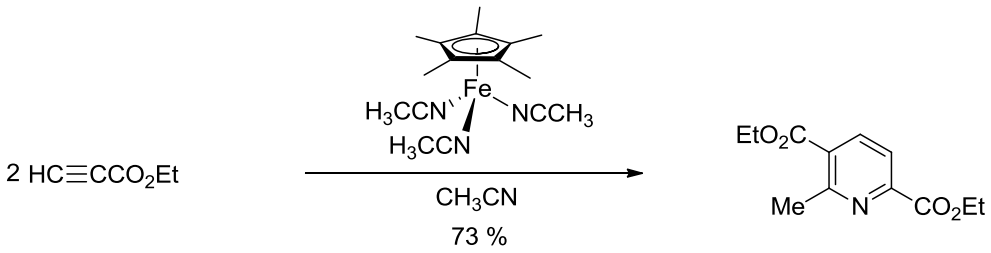


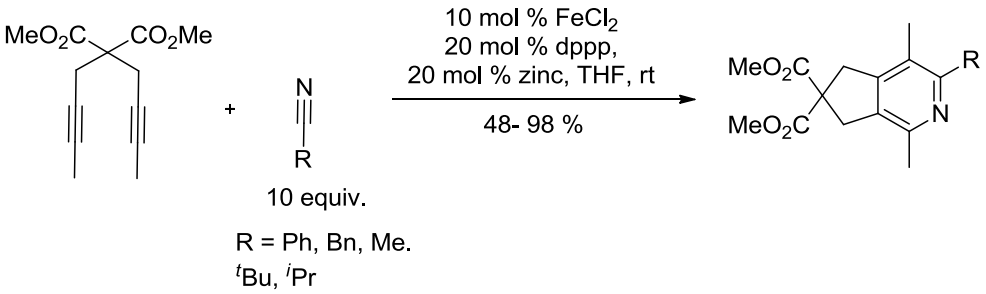
Figure 3.1 Sir William Ramsay's 1877 method to synthesize pyridine



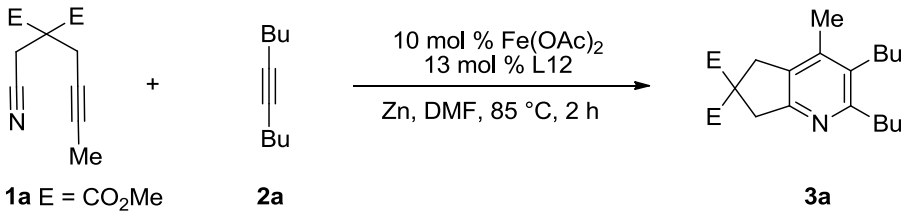
(3.10)



(3.11)



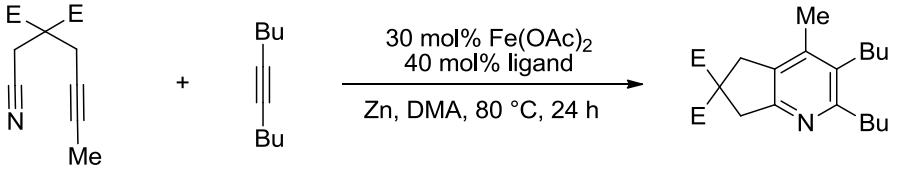
(3.12)



(3.13)

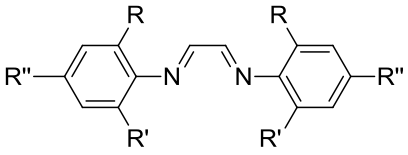
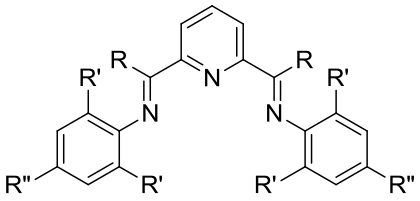
1a E = CO_2Me **2a** **3a**

Table 3.1 Ligand screen of alkynenitrile **1a** and decyne **2a**



(3.14)

1a E=CO_2Me **2a** **3a**

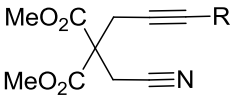
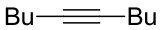
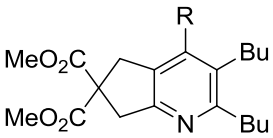
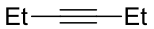
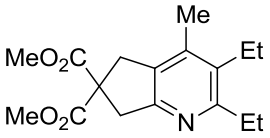
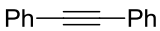
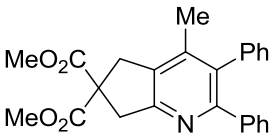
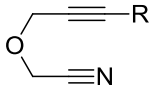
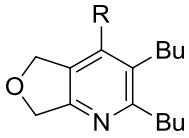
entry	ligand	conversion[b]	yield[b]
			
1	R = R' = R" = Me, L1	100	13
2	R = Me, R' = R" = H, L2	58	0
3	R = R' = ^{t}Bu, R" = H, L3	40	0
4	R = ^{t}Bu, R' = R" = H, L4	36	0
5	R = Et, R" = R" = H, L5	89	17
6	R = R' = ^{i}Pr, R" = H, L6	100	47
			
7	R = Me, R' = R" = Me, L7	43	0
8	R = Me, R' = ^{i}Pr, R" = H, L8	63	2
9	R = H, R' = R" = Me, L9	100	84
10	R = H, R' = ^{i}Pr, R" = H, L10	42	0
11	R = H, R' = Me, R" = OBn, L11	100	62[c]
12	**R = H, R' = ^{i}Pr, R" = OBn, L12**	**100**	**95[c]**

[a] Reaction conditions: 30 mol % $Fe(OAc)_2$, 40 mol % ligand, 40 mol % Zn, 0.1 M DMA, 80 °C, 24 h.

[b] Determined by gas chromatography with naphthalene as internal standard.

[c] Reaction conditions: 20 mol % $Fe(OAc)_2$, 27 mol % ligand, 22 mol % Zn, 0.1 M DMA, 80 °C.

Table 3.2 Substrate scope of alkynenitriles with symmetrical alkynes

entry	alkynenitrile	alkyne	time	product (% yield)[b]
				
1	R = Me, **1a**	**2a**	2h	**3a**, 70
2	R = Et, **1b**	**2a**	26h	**3b**, 86
3	R = Ph, **1c**	**2a**	5h	**3c**, 75
4	R = H, **1d**	**2a**	26h	**3d**, 30
5	R = $SiMe_3$, **1e**	**2a**	6h	**3e**, 57
				
6	**1a**	**2b**	6h	**3f**, 71
				
7	**1a**	**2c**	5h	**3g**, 54[c]
				
8	R = Et, **1f**	**2a**	4h	**3h**, 41

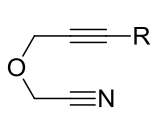
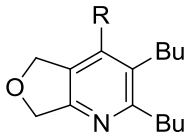
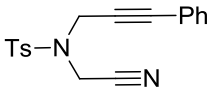
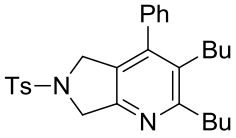
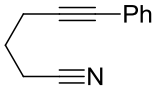
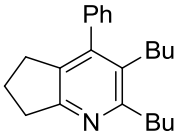
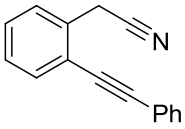
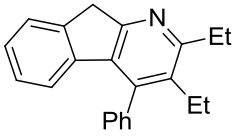
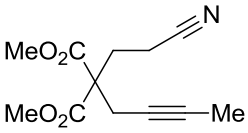
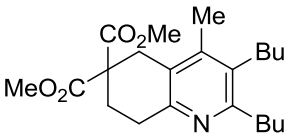
[a] Reaction Conditions: 0.4 M **1**, 0.4 M **2**, 10 mol % $Fe(OAc)_2$, 13 mol % **L12**, 20 mol % Zn, DMF, 85 °C.

[b] Average of at least two reaction runs.

[c] 2 equiv of alkyne.

[d] Reaction Conditions: 0.4 M **1**, 0.4 M **2**, 20 mol % $Fe(OAc)_2$, 26 mol % **L12**, 40 mol % Zn, DMF, 85 °C.

Table 3.3 More substrate scope of alkynenitriles with symmetrical alkynes

entry	alkynenitrile	alkyne	time	product (% yield)[b]
1	 R = Ph, **1g**	**2a**	4h	 **3i,** 45
2	 **1h**	**2a**	4h	 **3j**, 41
3	 **1i**	**2a**	4h	 **3k**, 65
4	 **1j**	**2b**	4h	 **3l**, 64
5	 **1k**	**2a**	24h	 **3m**, 40[d]

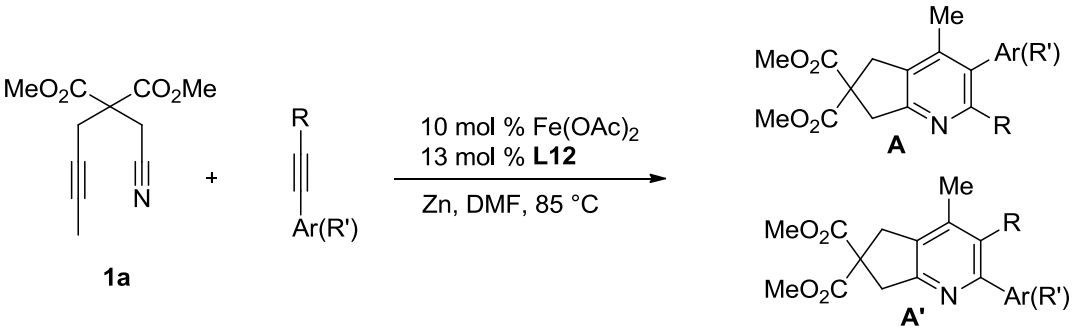
[a] Reaction Conditions: 0.4 M **1**, 0.4 M **2**, 10 mol % $Fe(OAc)_2$, 13 mol % **L12**, 20 mol % Zn, DMF, 85 °C.

[b] Average of at least two reaction runs.

[c] 2 equiv of alkyne.

[d] Reaction Conditions: 0.4M **1**, 0.4 M **2**, 20 mol % $Fe(OAc)_2$, 26 mol % **L12**, 40 mol % Zn, DMF, 85 °C.

Table 3.4 Cycloaddition of alkynenitrile **1a** and unsymmetrical alkynes



(3.14)

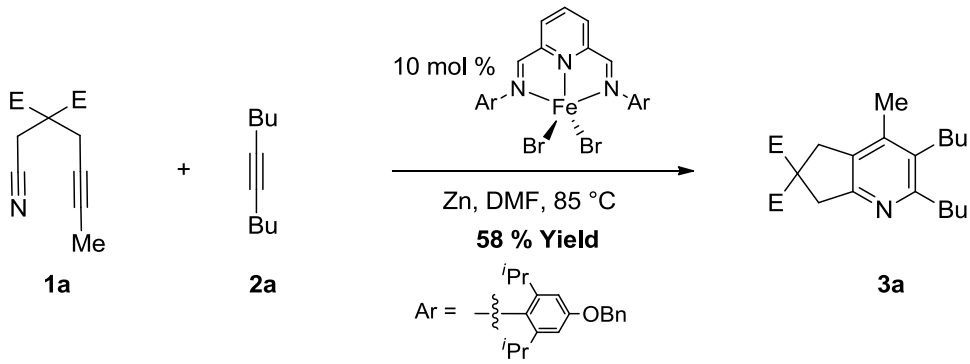
entry	alkyne	reaction time	product % yield (**A**:**A'**)[b]
	R—≡—Ar		
1	Ar = Ph, R = Me **2d**	6h	**3n,** 69 (1.2:1)
2	Ar = *p*-OMeC$_6$H$_4$, R = Me, **2e**	6h	**3o,** 39 (3:2)
3	Ar = *p*-CF$_3$C$_6$H$_4$, R = Me, **2f**	6h	**3p,** 39 (4:1)
4	Ar = Py, R = Me, **2g**	16h	**3q,** 56 (7:3)
5	Ar = Ph, R = Bu, **2h**	5h	**3r,** 53 (2:3)
6	Ar = Ph, R = -(CH$_2$)$_2$NTsBoc **2i**	5h	**3s**, 44 (3:2)
	R—≡—R'		
7	R = Me, R' = Bu, **2j**	24h	**3t**, 62 (1:1)
8	R = Me, R' = ^{t}Bu, **2k**	6h	**3u**, 26 (0:1)

[a] Reaction Conditions: 0.4 M **1**, 0.4 M **2**, 10 mol % Fe(OAc)$_2$, 13 mol % **L12**, 20 mol % Zn, DMF, 85°C.

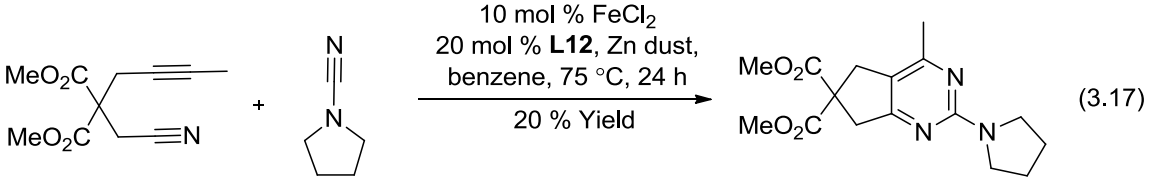
[b] Average of at least two reaction runs.


MeO2C CO2Me
N
Me
MeO2C CO2Me
1l
20 mol % Fe(OAc)2
32 mol % L12
Zn, DMF, 100 °C, 24 h
74 % Yield
MeO2C CO2Me
Me
N
CO2Me
CO2Me
3v

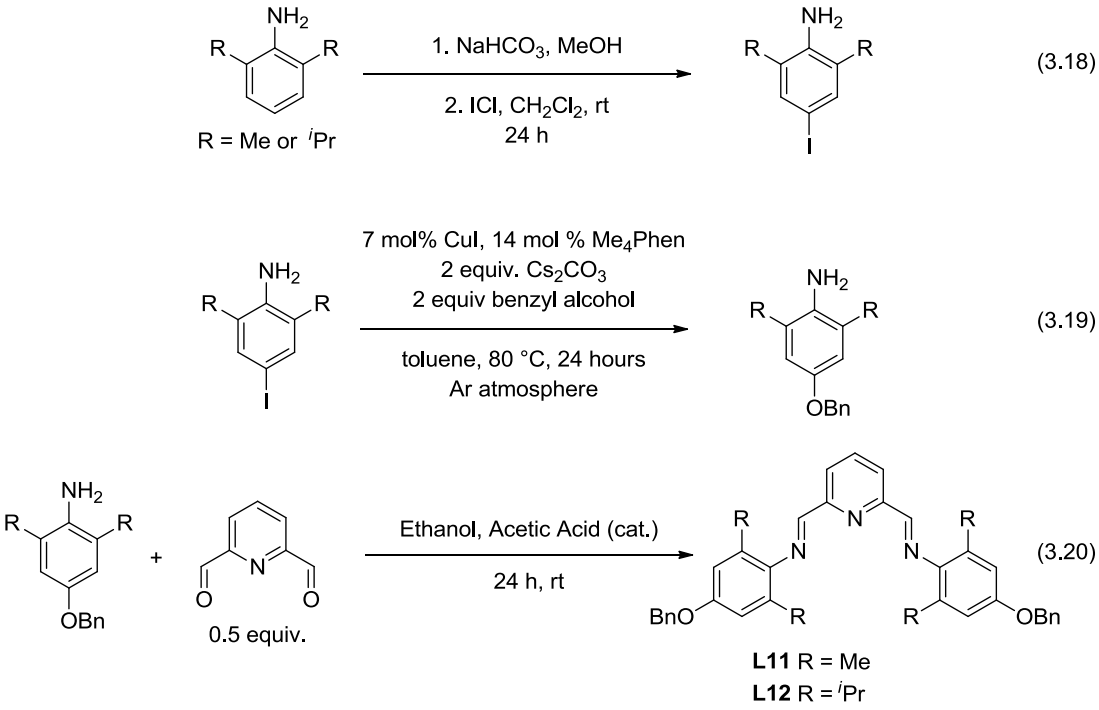
(3.15)

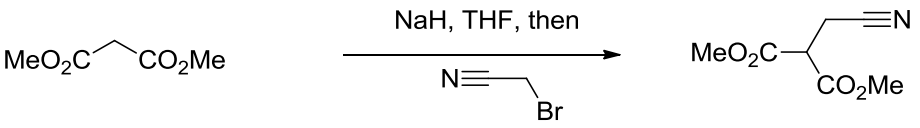

E E
N
Me
1a
+
Bu
Bu
2a
10 mol %
N
Ar N Fe N Ar
Br Br
Zn, DMF, 85 °C
58 % Yield
Ar = iPr OBn iPr
Me
E
E
Bu
N
Bu
3a

(3.16)

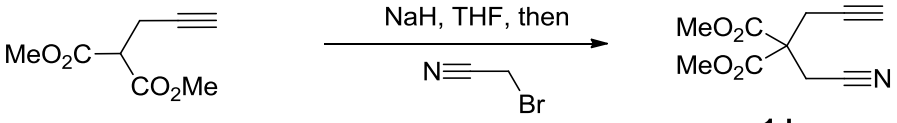


Scheme 3.3 Synthesis of ligands **L11-L12**





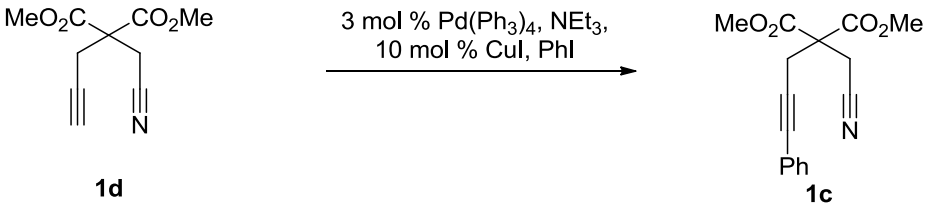
(3.21)



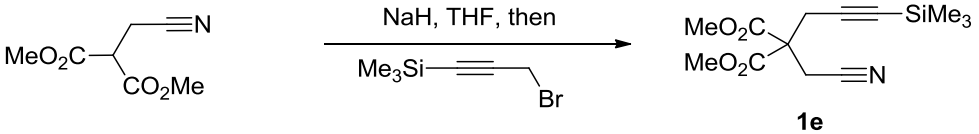
(3.22)

dimethyl-2-(prop-2-yn-1-yl)malonate

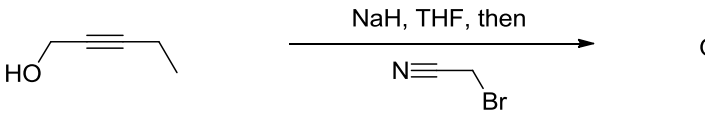
1d



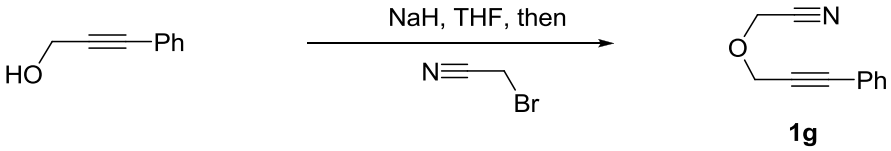
1d **1c** (3.23)



1e (3.24)

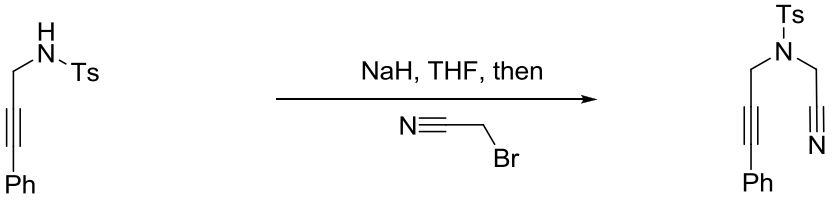


1f (3.25)



1g

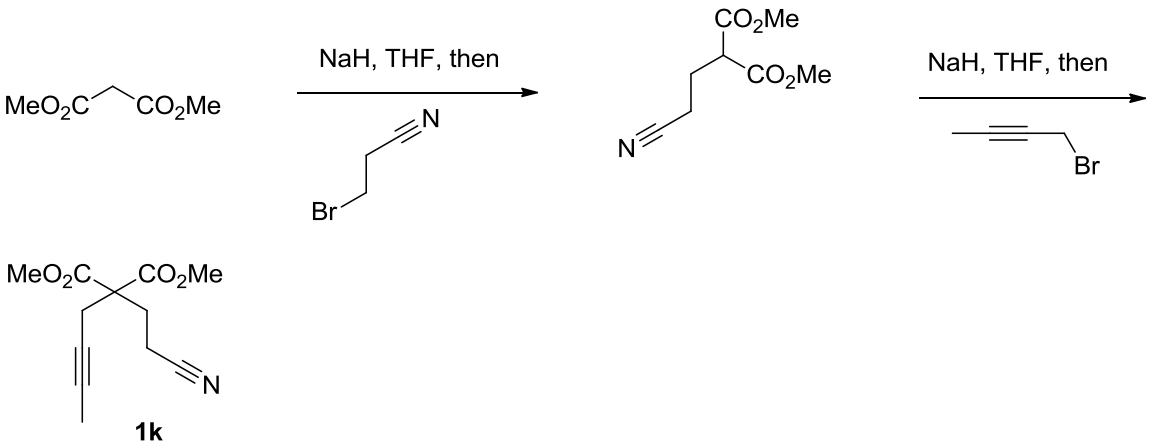
(3.26)



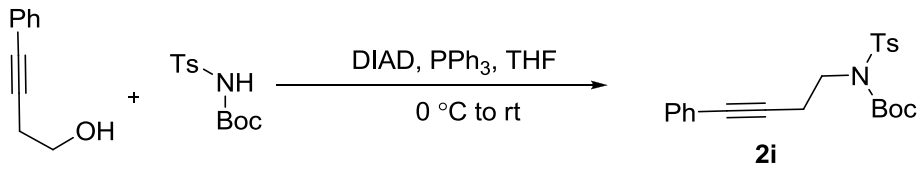
1h

(3.27)

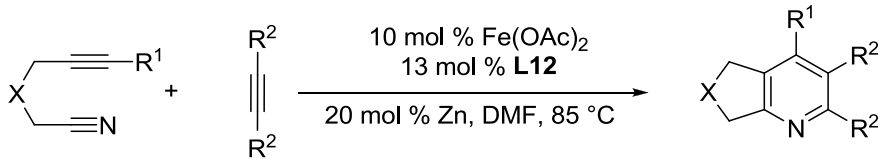
Scheme 3.4 Two-step preparation of **1k** from dimethylmalonate and bromoacetonitrile



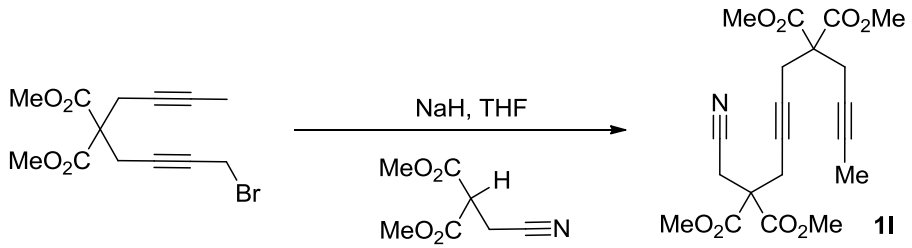
1k


Ph
OH
Ts
NH
Boc
DIAD, PPh3, THF
0 °C to rt
Ts
N
Boc
Ph
2i

(3.28)


R1
X
N
R2
R2
10 mol % Fe(OAc)2
13 mol % L12
20 mol % Zn, DMF, 85 °C
R1
R2
X
N
R2

(3.29)


MeO2C
MeO2C
Br
NaH, THF
MeO2C
H
MeO2C
N
MeO2C
CO2Me
N
Me
MeO2C
CO2Me
1l

(3.30)

References

1) Pyridine containing natural products: Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell:Oxford, **2000**.

2) Trost, B. M. *Science*, **1991**, *254*, 1471.

3) Reviews of cycloaddition : (a) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. b) Chopade, P.; Louie, J. *Adv. Synth. Catal*. **2006**, *348*, 2307. c) Schore, N. *Chem. Rev.* **1988**, *88*, 1081. d) Nakamura, I.; Yamamoto, Y. *Chem. Rev*. **2004**, 104, 2127. e) Varela, J. A.; Saá, C. *Synlett*. **2008**, 2571.

4) Cobalt catalyzed cycloaddition reactions: a) Wakatsuki, Y.; Yamazaki, H.; *J. Chem. Soc. Chem. Commun.* **1973**, 280. b) Brien, J. D.; Naiman, A.; Vollhardt, P. K. C. *J. Chem. Soc. Chem. Commun.* **1982**, 133-134. c) Varela, J. A, Castedo, L.; Saá, V. *Org. Lett*. **1999**, *1*, 2141. d) Fatland, A. W.; Eaton, B. E. *Org. Lett*. **2000**, *2*, 3131. e) Zhou, Y.; Porco, J. A. *Jr*.; Snyder, J. K. *Org. Lett*. **2007**, *9*, 393. f) Varela, J. A.; Castedo, L.; Saá, V. *J. Org. Chem*. **1997**, *62*, 4189. g) Heller, B.; Sundermann, B.; Fischer, C.; You, J. S.; Chen, W. Q.; Drexler, H. J.; Knochel, P.; Bonrath, B.; Gutnov, A. *J. Org. Chem*. **2003**, *68*, 9221. h) A. Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem*. **2004**, *116*, 3883. i) Gutnov, A.; Abaev, V.; Redkin, D.; Fischer, C.; Bonrath, W.; Heller, B. *Synlett* **2005**, *7*, 1188. j) Moretto, A. F.; Zhang, H-C.; Maryanoff, B. E.; *J. Am. Chem. Soc.* **2001**, *123*, 3157. k) Boñaga, L. V. R.; H.-C. Zhang, H-C.; Moretto, A. F.; Ye, H.; Gauthier, D. A.; Li, J.; Leo, G. C.; Maryanoff, G. C.; B. E. *J. Am. Chem. Soc*. **2005**, *127*, 3473. l) Chang, H-T.; Jeganmohan, M.; Cheng, C-H. *Org. Lett*. **2007**, *9*, 505.

5) Rhodium-catalyzed cycloaddition reactions: a) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem*. **2006**, 3917; b) Tanaka, K.; Hara, H.; Nishda, G.; Hirano, M. *Org. Lett*. **2007**, *9*, 1907. c) Wada, A.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett*. **2007**, *9*, 1295. d) Shibata, T.; Uchiyama, T.; Endo, K. *Org. Lett*. **2009**, *11*, 3906. e) Komine, Y.; Tanaka, K. *Org. Lett*. **2010**, *12*, 1312.

6) Ruthenium catalyzed cycloaddition reactions: a) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc*. **2001**, *123*, 6189. b) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun*. **2001**, 1102. c) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc*. **2005**, *127*, 605. d) Yamamoto, Y.; Kinpara, K.; Nishiyama, H.; Itoh, K. *Adv. Synth. Catal*. **2005**, *347*, 1913. e) Yamamoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. Eur. J*. **2006**, *12*, 5618.

7) Nickel-catalyzed cycloaddition reactions: a) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. *J. Am. Chem. Soc*. **2005**, *127*, 5030; b) T. N. Tekavec, T. N.; G. Zuo, G.; K. Simon, K.; J. Louie, J. *J. Org. Chem*. **2006**, *71*, 5834

8) Tantalum in cycloaddition reactions: Takai, K.; Yamada, M.; Utimoto, K. *Chem. Lett*. **1995**, 851

9) (a) Cross coupling using iron: a) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev*. **2004**, *104*, 6217. (b) Correa, A.; Garcia, M. O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (c) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6010

10) Oxidations using iron: a) *Iron Catalysis in Organic Chemistry: Reactions and Applications*; Pleitker, O.B., Ed; Wiley-VCH Weinheim, 2008. b) Chen, M.S. White, M. C. *Science* **2010**, *327*, 566. (c) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (d) Chen, K.; Que, Jr.; L. *Chem. Commun*. **1999**, 1375. (e) Kim, C.; Chen, K.; Kim, J.; Que, Jr. *J. Am. Chem. Soc*. **1997**, *119*, 5964. (f) Okuno, T.; Ito, S.; Ohba, S.; Nishida, Y. *J. Chem. Soc. Dalton Trans*. **1997**, 3547. (g) Groves, J.T.; Viski, P. *J. Am. Chem. Soc*. **1989**, *111*, 8537. (h) Khenkin, A. M.; Shilov, A.E. *New J. Chem*. **1989**, *13*, 659.

11) Polymerization reactions using iron: (a) Ouchi, M.; Terashima, T.; Mitsuo, S. *Chem. Rev.* **2009**, *109*, 4963. (b) Louie, J.; Grubbs, R. H. *Chem. Commun.* **2000**, 1479. (c) Britovsek, G. J. P.; Bruce, M.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; Mastroianni, S.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Strömberg, S.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728. (d) Small, B. L.; Brookhart, M.; Bennett, A. M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4049

12) Iron catalysts for benzene synthesis: (a) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organomet. Chem.* **2006**, *691*, 3129. (b) Breschi, C.; Piparo, L.; Pertici, P.; Maria Caporusso, A.; Vitulli, G. *J. Organomet. Chem.* **2000**, *607*, 57. (c) Fürstner, A.; Majima, K.; Martin, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann Christian, W. *J. Am. Chem. Soc.* **2008**, *130*, 1992. (d) Gonzalez-Arellano, C.; Balu, A. M.; Luque, R.; MacQuarrie, D. J. *Green Chemistry* **2010**, *12*, 1995. (e) Saino, N. ; Kogure, D.; Okamoto, S. *Org. Lett.* **2005**, *7*, 3065

13) a) Ramsay, W. *Philos. Mag.* **1876**, *2*, 269. (b) Ramsay, W. *Philos. Mag.* **1877**, *4*, 241

14) a) Knoch, F.; Kremer, F.; Schmidt, U.; Zenneck, U.; Le Floch, P.; Mathey, F. *Organometallics* **1996**, *15*, 2713. (b) Ferré, K.; Toupet, L.; Guerchais, V. *Organometallics* **2002**, *21*, 2578. c) Wang, C.; Li, X.; Wu, F.; Wan, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 1-6.

15) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794. (b) Sylvester, K. T.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8772. (c) Moreau, B. t.; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337. (d) Wu, J. Y.; Moreau, B. T.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 12915

16) Gibson, V. C.; Redshaw, C.; Solan, G. A. *Chem. Rev.* **2007**, *107*, 1745. (b) Fernández, I.; Trovitch, R. J.; Lobkovsky, E.; Chirik, P. *Organometallics* **2008**, *27*, 109. (c) Trovitch, R. J.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 11631. d) Small, B. L.; Brookhart, M.; Bennett, A. M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4049

17) Koroleva, E.V.; Gusak, K. N.; Ignatovich, Zh. V. *Russian Chemical Reviews* **2010**, *79*, 655

18) Synthesis of alkynenitrile **1a** and **1b** a) Miura, T.; Nakazawa. H.; Murakami, M. *Chem. Commun.* **2005**, 2855-2856. b) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642-13643

19) Synthesis of alkynenitrile **1i**: Shen, H.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 11473-11480

20) Synthesis of alkynenitrile **1j**: Lauritsen, A.; Madsen, R. *Org. Biomol. Chem.* **2006**, 4, 2898-2905.

21) Ligand synthesis: a) Saino, N.; Kogure, D.; Kase, K.; Okamoto, S. *J. Organometal. Chem.* **2006**, *691*, 3129. (b) Britovsek, G. J. P.; Bruce, M.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; Mastroianni, S.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Stroemberg, S.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728

22) Degnan, A. P.; Chaturvedula, P. V.; Conway, C. M.; Cook, D. A.; Davis, C. D.; Denton, R.; Han, X.; Macci, R.; Mathias, N. R.; Moench, P.; Pin, S. S.; Ren, S. X.; Schartman, R.; Signor, L. J.; Thalody, G.; Widmann, K. A.; Xu, C.; Macor, J. E.; Dubowchik, G. M. *J. Med. Chem.* **2008**, *51*, 4858. (b) Knox, J. R.; Toia, R. F.; Casida, J. E. *J. Agric. Food Chem.* **1992**, *40*, 909. (c) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284.

23) Tekavac, T.; Louie, J. *J. Org. Chem.* **2008**, *73*, 2641

24) Synthesis of alkynenitrile **1j**: Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2000**, 3007-3011

25) Synthesis of alkynenitrile **1k**: Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. *J. Mol. Catal. A: Chem.* **2008**, *292*, 44-48

26) Mori, S.; Yanase, T.; Aoyagi, S.; Monguchi, Y.; Maegawa, T.; Sajiki, H. *Eur. Chem. J.* **2008**, *14*, 6994-6999

27) a) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094-1095. b) Bennacer, B.; Fujiwara, M.; Lee, S-Y.; Ojima, I. *J. Am. Chem. Soc.* **2005**, *127*, 17756-17767.

28) Small, B. L.; Brookhart, M.; Bennett, A. M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4049.

CHAPTER 4

IRON-CATALYZED CYCLOADDITION OF DIYNES AND CYANAMIDES

Introduction

The presence of nitrogen containing heterocycles is highly prevalent in various natural products and pharmaceutically active compounds[1] (Figure 4.1). Developing synthetic methods that provide access to such compounds in an efficient manner is highly significant. Our recent success in the cycloaddition of alkynenitriles and alkynes to access substituted pyridines[2] using a cheap, less-toxic, and cost effective iron source prompted us to investigate methodologies that could access other pyridine containing compounds. 2-Aminopyridines are important structural cores present in a number of natural products and biologically active compounds.[1] Substituted 2-aminopyridine scaffolds also functions as ligands[3] in organometallic chemistry. The earliest example of the synthesis of 2-aminopyridines involves the reaction of 2-pyridones[4a] and amines (Equation 4.1). 2-Aminopyridines were isolated in low yields by this method.

The reaction also required the use high temperature and pressure. Another common method to synthesize 2-aminopyridines is by the reaction of a primary or secondary

amines and 2-halopyridines. Hirota[4b] reacted 2-halopyridines and a secondary amine in the presence of zinc chloride/zinc to effectively synthesize 2-aminopyridines in good yields (Equation 4.2). However, this method also requires elevated temperatures (180 °C). Another method to synthesize substituted 2-aminopyridines by reacting α,β-unsaturated carbonyl compounds,[4c] 2-(benzotriazol-1-yl)acetonitrile, and secondary amines (Equation 4.3). Buchwald[4d] synthesized 2-aminopyridine derivatives at room temperature utilizing a cross-coupling approach between a 2-bromopyridine and a secondary amine in the presence of catalytic palladium (Equation 4.4).

The earliest cycloaddition method to prepare to 2-aminopyridines was reported by Bönneman[5] using CpCoCOD as the catalyst (Equation 4.5) under ultra-violet light. This was followed by a broader substrate scope report by Heller[6] using an alternative cobalt-based catalyst which also required ultra-violet (UV) radiation for activation of the catalyst. The 2-aminopyridines were obtained in moderate yields (Equation 4.6). Maryanoff[7a] carried out a more detailed study of the cycloaddition of diynes and cyanamides to afford 2-aminopyridines in good yields using 15 mol % cobalt-catalyst loading (Equation 4.7). Macrocyclic[7b] frameworks can also be accessed using the same cobalt-catalyst system. Tanaka demonstrated that by using a cationic rhodium catalyst[8] 2-aminopyridines can be prepared (equation 4.8). However, the methodology was applied to only one example albeit in low yield.

The significance of 2-aminopyridine structural motifs prompted us to develop an efficient methodology that can synthesize these molecules in a single step from simple and easily accessible starting material. We envisioned a strategy using [2+2+2] cycloaddition chemistry between easily accessible diynes and cyanamides. Our group

has reported the cycloaddition reaction of diynes and various cyanamides (Equation 4.9) using a Ni-NHC catalyst system.[9] A Fe-catalyzed methodology to access 2-aminopyridines has not yet been reported. We are interested in developing a synthetic methodology which would synthesize such structural cores in a single synthetic step using relatively inexpensive, easily available iron salts.

Results and Discussion

With the success in the iron-catalyzed cycloaddition of alkynenitriles[2] and alkynes to afford pyridines, we decided to test the utility of the iron-catalytic system in the cycloaddition reaction of diynes and cyanamides. We were particularly skeptical of this cycloaddition due to the tendency of diynes to dimerize under metal catalyzed cycloaddition reaction.[10] In collaboration with another graduate student Timothy Lane, diyne **1a** and pyrrolidine cyanamide **2a** were subjected to 5 mol % iron chloride, 10 mol % ligand, 10 mol % zinc dust in benzene as solvent at 75 °C. Various ligands were screened. Monodendate triphenylphosphine (Table 4.1, entry 1) did not afford any cycloaddition product. Bidendate phosphines (Table 4.1, entries 2 and 3) proved ineffective in this cycloaddition reaction with no cycloaddition product formation. Sterically hindered bisimine ligand **L1** afforded some of the desired cycloaddition product in low yields and 2, 4, 6-trimethylphenylsubstituted bisimine **L2** gave moderate conversions of starting material and low yields for the desired cycloaddition product (Table 4.1, entries 4-5). Aldehyde and ketone derived bis(imino)pyridyl ligands used in previous cycloaddition reactions[11] were also tested. Ketimine-based bis(imino)pyridine

ligand **L3** did not afford the desired cycloaddition product (Table 4.1, entry 6). Bis(aldimino)pyridyl ligand **L4** with no substitution on the aryl ring does not afford any cycloaddition product (Table 4.1, entry 7). *ortho*-Disubstituted bis(aldimino)pyridyl ligands afforded the desired cycloaddition product with full conversion of diyne and excellent GC yields (Table 4.1, entries 8-10). Sterically bulkier *o*-diisopropylsubstitued bis(aldimino)pyridyl ligand **L5**. The electron rich *p*ara-benzyloxy-substituted bis(aldimino)pyridyl **L6** provided full conversion of starting material to products. The highest isolated yield of 86% was obtained with trimethyl substituted bis(aldimino)pyridyl ligand **L7** (Table 4.1, entry 10).

With our optimized reaction conditions (5 mol % $FeCl_2$, 10 mol % **L7**, and 10 mol % zinc at 75 °C in benzene) for the 2-aminopyridine product formation in hand, the substrate scope of the diyne functionality in the reaction was evaluated. Various diynes were prepared and their reactivity in the cycloaddition reaction was tested. The nitrogen backbone diyne **1a** and pyrrolidine cyanamide **2a** yielded 86 % of 2-aminopyridine product (Table 4.2, entry 1). Terminal diynes which are known to undergo oligomerization under transition metal-catalyzed reaction conditions react in this cycloaddition reaction afforded 48 % of the 2-aminopyridine product in this cycloaddition reaction (Table 4.2, entry 2). Methyl-substituted internal diyne **1c** reacted with cyanamide **2a** under the iron-catalyzed reaction conditions affording the 2-aminopyridine product in 73 % yield (Table 4.2, entry 3). Six-membered fused bicyclic 2-aminopyridines were also be prepared using internally substituted tetraester diyne **1d** and cyanamide **2a** to yield the cycloaddition product in 79 % yield over 5 h as compared with diyne **1c** (Table 4.2, entry 4 v/s entry 3).

Various other diynes were also tested in the cycloaddition reactions with *N*-cyanopyrrolidine **2a**. The cycloaddition of diyne **1e** (Figure 4.2) devoid of substitution on the backbone (without the Thorpe-Ingold assistance)[12] and cyanamide **2a** did not afford the corresponding 2-aminopyridine product. Only the starting material diyne **1d** was isolated. Also, diyne **1f** with a sulfoxide backbone, diyne **1g** with terminal phenyl groups, and diyne **1h** with bulky trimethylsilyl groups did not undergo any reaction with cyanamide **2a** (Figure 4.2).

Next, the substrate scope of the cyanamide functionality was tested by treating various cyanamides with diyne **1c**. *N*-Cyanopiperdine **2b** yields the corresponding aminopyridine with diyne **1d** albeit in slightly lower yield compared with the *N*-cyanopyrrolidine **2a** (Table 4.2, entry 3 v/s Table 4.3, entry 1). Activated *N*-cyanomorpholine **2c** afforded low yield of the cycloaddition product when used with the cobalt-catalyst system.[7c] However, under our optimized reaction conditions **2c** reacts with diyne **1c** to afford 84 % yield of the desired 2-aminopyridine product (Table 4.3, entry 3). *N*-dimethylcyanamide **2d** undergoes cycloaddition with diyne **1c** to afford the desired cycloaddition product in 82 % yield (Table 4.3, entries 4). However, changing the *N*-alkyl substituents on the cyanamide to ethyl drastically reduced the yield of the 2-aminopyridine cycloaddition product (Table 4.3, entry 4 v/s entry 3). *N*-phenyl-methylcyanamide **2f** reacted with diyne **1c** under the optimized reaction conditions to afford the 2-aminopyridine product **3j** in 70 % yield (Table 4.3, entry 6) in a shorter reaction time as compared with sterically bulky *N*-cyanodibenzazepine **2g** (with a reaction time of 22 h), affording the corresponding 2-aminopyridine product in 69 % yield.

Bis(aldimine)pyridyl ligands proved superior to the various phosphines that were tested in this cycloaddition.In some cases the diyne dimerization is significant which adversely affected the overall yield of the desired 2-aminopyridine product. Our reaction procedure requires the addition of the diyne moiety slowly to the mixture of cyanamide, iron chloride and ligand over 1 h. We postulate that by the addition of the diyne moiety in about 3 h could minimize this dimerization. Attempts are being made to reduce the amount of cyanamides used in the cycloaddition reaction from 2 equiv. to 1.2 equiv. Unsymmetrical diynes could also be tested in this cycloaddition reaction. Based on previous reports,[11] we are attempting to isolate the iron chloride-L7 complex precatalyst and test its catalytic efficiency in the cycloaddition reaction. If the isolation of the iron-ligand complex precatalyst is successful, we would subject the iron-ligand complex to Na-Hg (as previously reported) reduction[15] and attempt to isolate the iron in a lower oxidation state. Using this reduced complex in the cycloaddition reaction might shed some light on the possible oxidation state of the iron during the catalysis.

Conclusions

We have successfully developed an iron-catalyzed reaction to synthesize 2-aminopyridine from simple starting materials by the reaction with diynes and cyanamides. This method affords the desired 2-aminopyridines in moderate to excellent yields under mild conditions. This is the first reported example of the synthesis 2-aminopyridines using an iron-based catalyst system.

Experimental

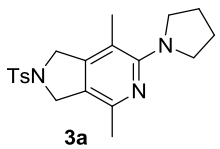
All reactions were conducted under inert atmosphere conditions using standard Schlenk techniques or in a N_2 filled glove-box unless otherwise noted. Benzene was dried over neutral alumina under N_2 using a Grubbs-type solvent purification system. THF was freshly distilled from Na/benzophenone. Iron chloride anhydrous (99.95 % purity) was purchased from Alfa Aeasar. Diynes **1a-1c**[3], **1f**[17] were prepared by known literature procedures. Ligands L1-L7 were prepared by an earlier known literature procedures.[5] All cyanamides were purchased from Sigma Aldrich. The liquid cyanamides were degassed by the freeze-pump-thaw technique and taken in the dry box and used. ^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 MHz and 300 MHz unless otherwise noted. ^{1}H NMR was recorded on an Inova-400 and Varian VXL-300 spectrometers. All spectra are referenced to residual proteated $CHCl_3$ via a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.26 ppm for ^{13}C. All ^{13}C NMR spectra are proton decoupled. The infra-red spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Gas Chromatography was performed on an Agilent 6890 gas chromatography with a 30 m HP-5 column using the following conditions: initial oven temperature:100 ºC; temperature ramp rate 10 ºC/min.; final temperature:300 ºC held for 12 min; detector temperature: 250 ºC. High Resolution Mass Spectrometry analyses were performed at the University of Utah Mass Spectrometry facility by Dr. James Müller.

General Procedure A for Cycloaddition

In a nitrogen filled glove box, 5 mol % $FeCl_2$ and 10 mol % **L7** were weighed out in a vial. Benzene was added and the reaction mixture was stirred for 10-15 min. Diyne, cyanamide, and zinc were added and the reaction was capped with a thermoset screw cap and placed in an oil bath at 75 °C. The reaction mixture was stirred at 75 °C till the reaction was complete (reaction was monitored by gas chromatography). The crude product was purified via flash silica gel chromatography.

General Procedure B for Cycloaddition

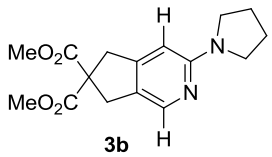
In a nitrogen filled glove box, 5 mol % $FeCl_2$ and 10 mol % **L7** were weighed out in a vial. Benzene was added and the reaction mixture was stirred for 10-15 min. Cyanamide and zinc were added and the reaction was capped with a teflon septa and screw cap and placed in an oil bath at 75 °C. A solution of diyne in benzene was added to the reaction mixture over a 1-2 h time period. After the addition was complete the reaction mixture was stirred at 75 °C till the reaction was complete (reaction was monitored by gas chromatography). The crude product was purified via silica gel flash chromatography.



3a

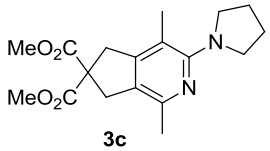
Synthesis of 4,7-dimethyl-6-(pyrrolidin-1-yl)-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (**3a**): Compound **3a** was prepared using the general procedure A with **1a** (100 mg, 0.36 mmol), **2a** (70 mg, 0.72 mmol), $FeCl_2$ (2.3 mg, 1.8 x 10^{-2} mmol), **L7** (13.4 mg, 3.6 x 10^{-2} mmol), and zinc (4.8 mg, 7.3 x 10^{-2} mmol) in 0.8 ml of benzene. The reaction was stirred at 75 °C for 1 h.

After the reaction was complete (reaction monitored by GC), the crude product was isolated by evaporation of solvent under reduced pressure and purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes (200 ml), then 15 % ethyl acetate in hexanes (300 ml) to yield **3a** (115.4 mg, 86 %) as a yellowish solid. Spectral data were compared with known literature values.[9]



3b

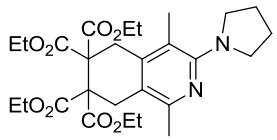
Synthesis of dimethyl 3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (**3b**): Compound **3b** was prepared using the general procedure A with diyne **1b** (100 mg, 0.48 mmol), **2a** (92 mg, 0.96 mmol), $FeCl_2$ (3.1 mg, 2.4 x 10^{-2} mmol), **L7** (17.7 mg, 4.8 x 10^{-2} mmol), and zinc (3.1 mg, 4.8 x 10^{-2} mmol) in 0.5 ml of benzene. The reaction was stirred at 75 °C for 5 h. After the reaction was complete (reaction monitored by GC), the crude product was isolated by evaporation of solvent and purified with silica gel flash chromatography using 20 % ethyl acetate in hexanes (200 ml), then 30 % ethyl acetate in hexanes (200 ml), then 30 % ethyl acetate in hexanes (200 ml), then 40 % ethyl acetate in hexanes (200 ml) to yield **3b** (45 mg, 45 %) as a yellowish solid. Spectral data were compared with known literature values.[9]



3c

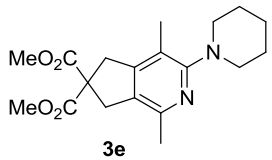
Synthesis of dimethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (**3c**): Compound **3d** was prepared using the general procedure B with **2a** (81 mg, 0.84 mmol), $FeCl_2$ (2.7 mg, 2.1 x 10^{-2} mmol), **L7** (15.6 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 0.4 ml of benzene. Diyne **1d** dissolved in 0.5 ml benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 4 h. After the reaction was complete (reaction monitored by GC), the crude product was isolated by evaporation

of solvent and purified by silica gel flash chromatography using 10 % ethyl acetate in hexanes (200 ml), then 15 % ethyl acetate in hexanes (300 ml) to yield **3d** (103 mg, 73 %) as a yellowish solid. Spectral data were compared with known literature values.[14]



3d

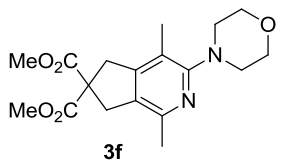
Synthesis of tetraethyl-1,4-dimethyl-3-(pyrrolidin-1-yl)isoquinoline-6,6,7,7(5H,8H)tetracarboxylate (**3d**): Compound **3d** was prepared using the general procedure B with **2a** (48 mg, 0.47 mmol), $FeCl_2$ (1.5 mg, 1.2 x 10^{-2} mmol), **L7** (8.7 mg, 2.4 x 10^{-2} mmol), and zinc (1.6 mg, 2.4 x 10^{-2} mmol) in 200 µL of benzene. Diyne **1c** dissolved in 0.4 ml benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 6 h. After the reaction was complete (reaction monitored by GC), the crude product was isolated by evaporation of solvent and purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes (200 ml), then 15 % ethyl acetate in hexanes (400 ml) to yield **3a** (98 mg, 80 %) as a yellowish solid. ^{1}H (400 MHz, $CDCl_3$): 4.24-4.10 (m, 8H), 3.35 (t, J = 7.6 Hz, 6H), 3.28 (s, 2H), 2.32 (s, 3H), 2.11 (s, 2H), 1.85 (quint, J = 6.8 Hz, 2H), 1.28-1.25 (m, 12H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 170.2, 170.1, 157.9, 150.2, 141.7, 118.2, 115.8, 62.2, 62.0, 61.9, 57.4, 57.1, 50.4, 33.1, 31.8, 25.5, 22.3, 14.8, 13.9. HRMS calculated for $C_{28}H_{27}N_2O_4$ 455.1971, found 455.1969.



3e

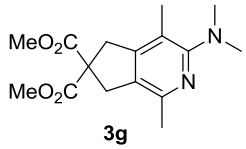
Synthesis of dimethyl-1,4-dimethyl-3-(piperidin-1-yl)-5H-cyclopenta[c]-pyridine-6,6-(7H)-dicarboxylate (**3e**): Compound **3e** was prepared using the general procedure B with **2a** (48 mg, 0.47 mmol), $FeCl_2$ (1.5 mg, 1.2 x 10^{-2} mmol), **L7** (8.7 mg, 2.4 x 10^{-2} mmol), and zinc (1.6 mg, 2.4 x 10^{-2} mmol) in 0.5 ml of benzene. Diyne **1c** (100 mg, 0.42 mmol) dissolved in 0.5 ml benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 4 h.

After the reaction was complete (reaction monitored by GC), the crude product was isolated by evaporation of solvent and purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes (200 ml), then 15 % ethyl acetate in hexanes (200 ml), and 20 % ethyl acetate and hexanes to yield **3e** (77 mg, 53 %) as a yellowish oil. ^{1}H (400 MHz, $CDCl_3$): 3.77 (s, 6H), 3.50 (s, 2H), 3.48 (s, 2H), 3.0 (t, J = 4.8 Hz, 4H), 2.33 (s, 2H), 2.14 (s, 2H), 1.68 (quint, J = 6 Hz, 4H), 1.58 (q, J = 7.2 Hz, 2H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 172.3, 161.8, 150.2, 148.3, 127.6, 118.3, 59.7, 53.3, 51.7, 40.1, 38.9, 26.6, 24.9, 21.9, 14.5.



3f

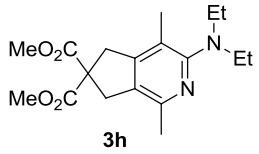
Synthesis of dimethyl-1,4-dimethyl-3-morpholino-5H-cyclopenta[c]pyridine-6,6-(7H)-dicarboxylate (**3f**): Compound **3f** was prepared using the general procedure B with **2a** (48 mg, 0.47 mmol), $FeCl_2$ (2.68 mg, 2.1 x 10^{-2} mmol), **L7** (15.6 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 0.2 ml of benzene. Diyne **1c** (50 mg, 0.21 mmol) dissolved in 0.4 ml benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 5 h. After the reaction was complete (reaction monitored by GC), the crude product was isolated by evaporation of solvent and purified with silica gel flash chromatography using 20 % ethyl acetate in hexanes (200 ml), then 30 % ethyl acetate in hexanes (400 ml) to yield **3f** (62 mg, 84 %) as a yellowish oil. Spectral data were compared with known literature values.[9]



3g

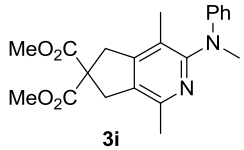
Synthesis of dimethyl-3-(dimethylamino)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3g**): Compound **3g** was prepared using the general procedure B with **2a** (60 mg, 0.85 mmol), $FeCl_2$ (2.68 mg, 2.1 x 10^{-2} mmol), **L7** (15.6 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x

10^{-2} mmol) in 0.5 ml of benzene. Diyne **1c** (100 mg, 0.42 mmol) dissolved in 0.5 ml benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 5 h. After the reaction was complete (reaction monitored by GC), the crude product was isolated by evaporation of solvent under reduced pressure and purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes (200 ml), then 15 % ethyl acetate in hexanes (400 ml) to yield **3g** (107 mg, 82 %) as a yellowish oil. Spectral data were compared with known literature values.[11]



3h

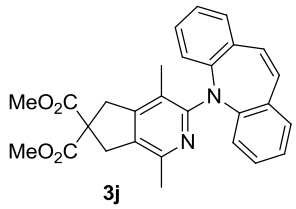
Synthesis of dimethyl-3-(diethylamino)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3h**): Compound **3h** was prepared using the general procedure B with **2a** (83 mg, 0.47 mmol), $FeCl_2$ (2.68 mg, 2.1 x 10^{-2} mmol), **L7** (15.6 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 0.4 ml of benzene. Diyne **1c** (50 mg, 0.21 mmol) dissolved in 0.5 ml benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 5 h. After the reaction was complete (reaction monitored by GC), the crude was isolated by evaporation of solvent and purified with silica gel flash chromatography using 20 % ethyl acetate in hexanes (200 ml), then 30 % ethyl acetate in hexanes (400 ml) to yield **3h** (31 mg, 22 %) as a yellowish oil. Spectral data were compared with known literature values.[9]



3i

Synthesis of dimethyl 1,4-dimethyl-3-(methyl(phenyl)amino)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3i**): Compound **3i** was prepared using the general procedure with **2a** (83 mg, 0.47 mmol), $FeCl_2$ (2.68 mg, 2.1 x 10^{-2} mmol), **L7** (15.6 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 0.6 ml of benzene. Diyne **1c** (50 mg, 0.21 mmol) dissolved in 0.5 ml

benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 4 h. After the reaction was complete (reaction was monitored by GC), the crude product was isolated by evaporation of solvent and purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes (200 ml), then 15 % ethyl acetate in hexanes (200 ml), 20 % ethyl acetate in hexanes (400 ml) to yield **3i** (110 mg, 70 %) as a yellowish oil. Spectral data were compared with known literature values.[9]



3j

Synthesis of dimethyl-3-(5H-dibenzo[b,f]azepin-5-yl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**3j**): Compound **3j** was prepared using the general procedure B with **2a** (83 mg, 0.47 mmol), $FeCl_2$ (2.68 mg, 2.1 x 10^{-2} mmol), **L7** (15.6 mg, 4.2 x 10^{-2} mmol), and zinc (2.8 mg, 4.2 x 10^{-2} mmol) in 0.6 ml of benzene. Diyne **1c** (50 mg, 0.21 mmol) dissolved in 0.5 ml benzene was added over 1.5 h. The reaction mixture was stirred at 75 °C for 22 h. After the reaction was complete (reaction was monitored by GC), the crude product was isolated by evaporation of solvent and purified with silica gel flash chromatography using 10 % ethyl acetate in hexanes to yield **3j** (133 mg, 69 %) as a yellowish solid. ^{1}H (400 MHz, $CDCl_3$): 7.71 (dd, J = 8 Hz, 0.8 Hz, 2H), 7.22 (dd, J = 8 Hz, 1.6 Hz, 2H), 7.16 (dd, J = 8 Hz, 1.6 Hz, 2H), 7.06 (dt, J = 7.2 Hz, 0.8 Hz, 2H), 6.85 (s, 2H), 3.75 (s, 6H), 3.44 (s, 2H), 2.44 (s, 3H), 1.78 (s, 3H). ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 172.2, 156.1, 151.7, 148.4, 148.1, 135.1, 132.4, 129.6, 128.8, 127.3, 124.7, 120.4, 59.8, 53.3, 40.3, 39.0, 22.1, 14.9.

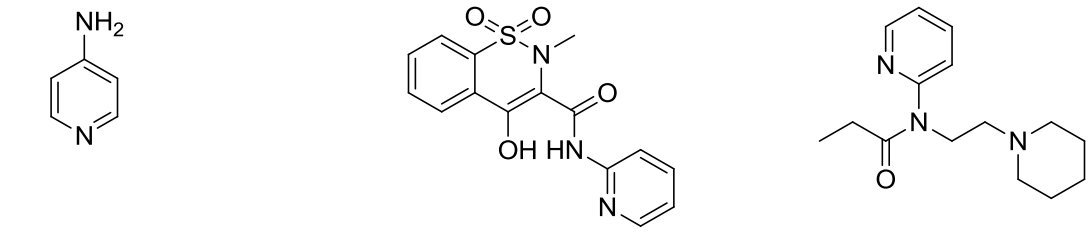
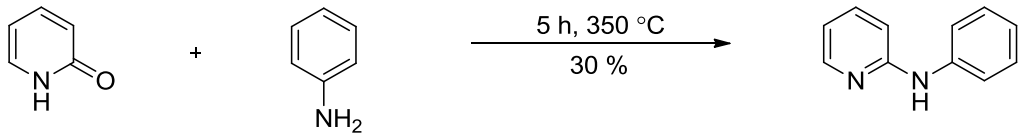
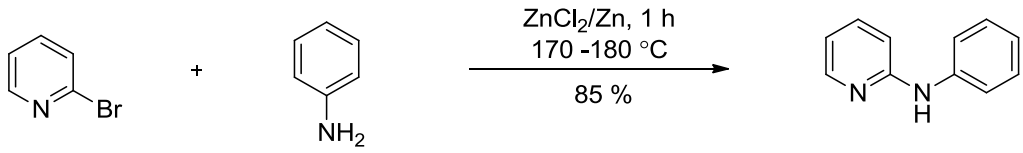


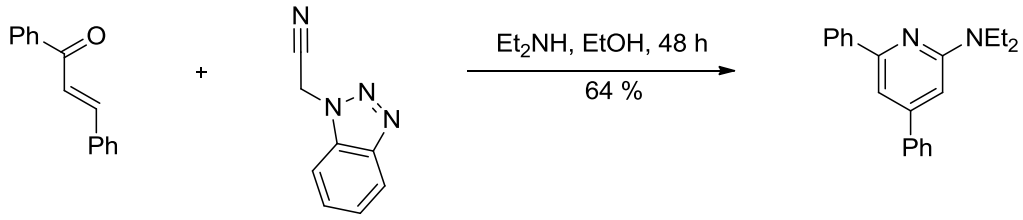
Figure 4.1 Aminopyridines in some biologically active compounds



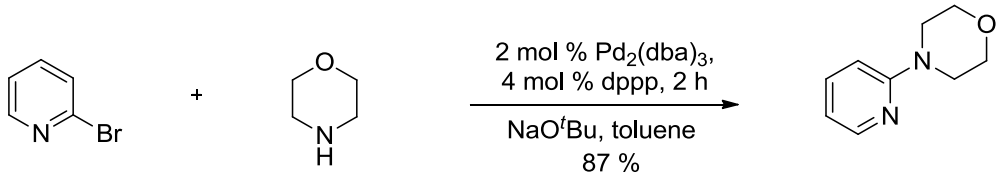
(4.1)



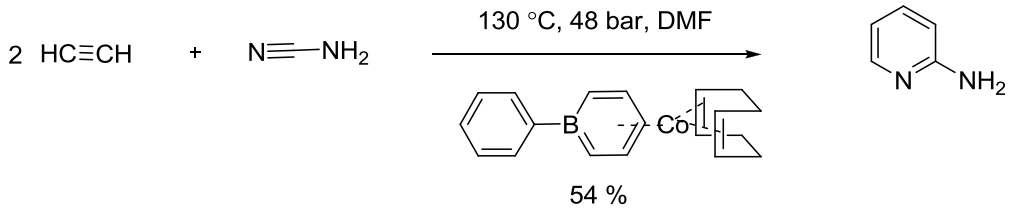
(4.2)



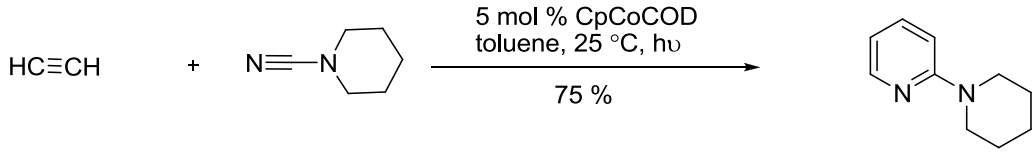
(4.3)


2 mol % Pd2(dba)3,
4 mol % dppp, 2 h
NaOtBu, toluene
87 %

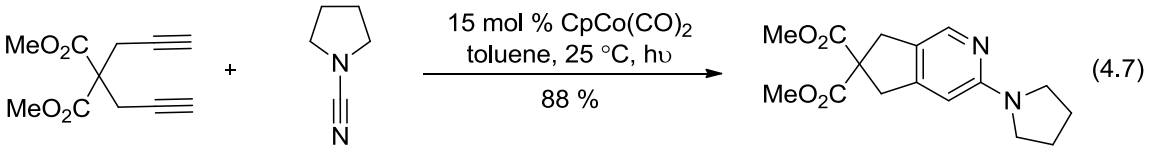
(4.4)


2 HC≡CH
130 °C, 48 bar, DMF
54 %

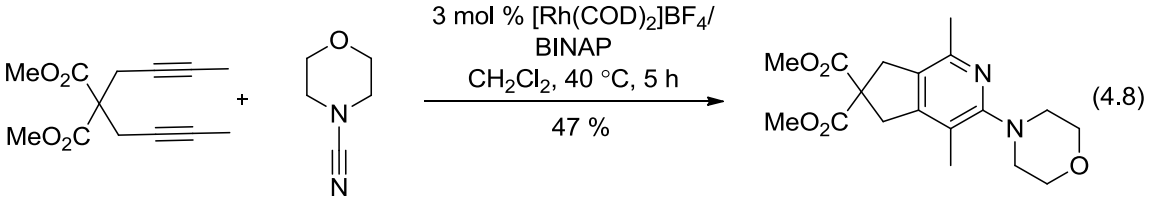
(4.5)


HC≡CH
5 mol % CpCoCOD
toluene, 25 °C, hυ
75 %

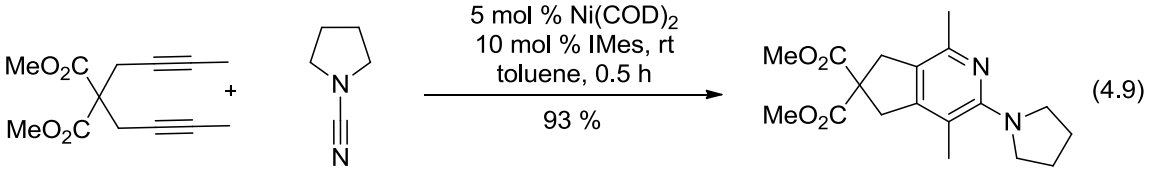
(4.6)


MeO2C
MeO2C
+
N
N
15 mol % CpCo(CO)2
toluene, 25 °C, hυ
88 %
MeO2C
MeO2C
N
N

(4.7)

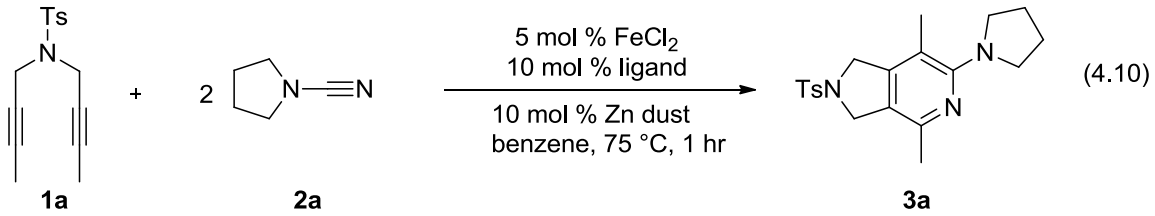

MeO2C
MeO2C
+
O
N
N
3 mol % [Rh(COD)2]BF4/
BINAP
CH2Cl2, 40 °C, 5 h
47 %
MeO2C
MeO2C
N
N
O

(4.8)


MeO2C
MeO2C
+
N
N
5 mol % Ni(COD)2
10 mol % IMes, rt
toluene, 0.5 h
93 %
MeO2C
MeO2C
N
N

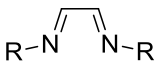
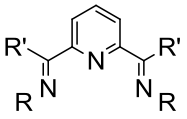
(4.9)

Table 4.1 Cycloaddition reaction of diyne **1a** and cyanamide **2a** with various ligands



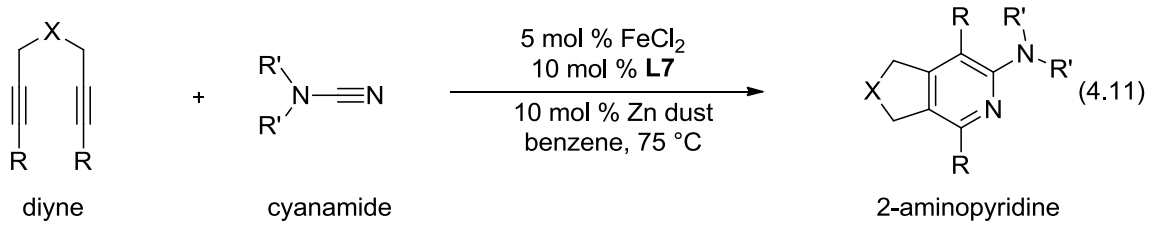
(4.10)

1a **2a** **3a**

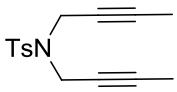
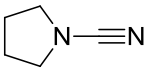
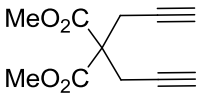
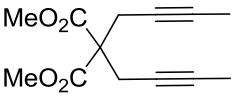
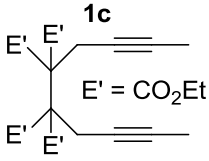
entry	ligand	% conversion [a]	% yield [a]
1	PPh_3	3	0
2	dppp	11	0
3	dppf	0	0
			
4	R = 2,6- diisopropylbenzene, **L1**	70	4
5	R = 2,4,6-trimethylbenzene, **L2**	94	44
			
6	R = 2,4,6-trimethylbenzene, R' = Me, **L3**	9	0
7	R= Ph, R' = H, **L4**	15	0
8	R = 2,6-diisopropylbenzene, R' = H, **L5**	>99	>99
9	R = 4-benzyloxy-2,6-diisopropylbenzene, R' = H, **L6**	>99	>99
10	**R = 2,4,6-trimethylbenzene, R' = H, L7**	**>99**	**>99 (86)[c]**

[a] determined by gas chromatography using naphthalene as internal standard

Table 4.2 Cycloaddition of *N*-cyanopyrrolidine with different diynes



diyne cyanamide 2-aminopyridine

entry	diyne	cyanamide	reaction time	% isolated yield
				
1	**1a**	**2a**	1 h	86, **3a**
				
2	**1b**	**2a**	5 h	45, **3b**
				
3	**1c**	**2a**	5 h	73, **3c**
				
4	**1d**	**2a**	30 h	79, **3d**

Reaction conditions: 0.4 M diyne, 0.8 M cyanamide, 5 mol % $FeCl_2$, 10 mol % L7, 10 mol % zinc, benzene at 75 °C

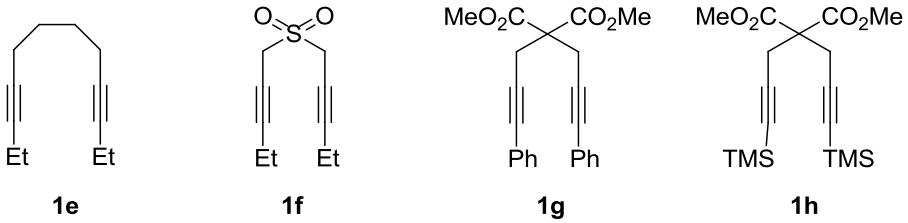
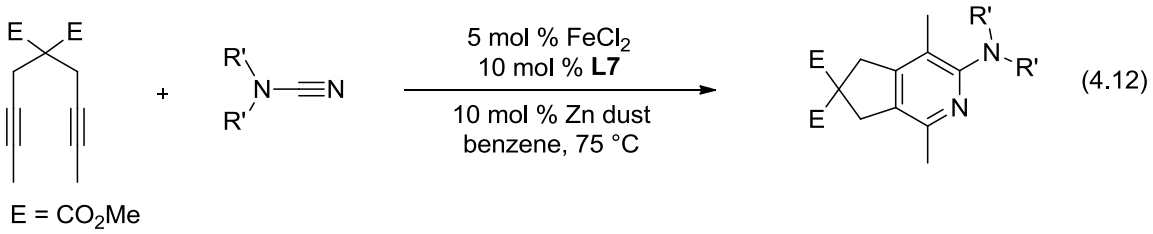


Figure 4.2 Diynes that are unreactive in the cycloaddition reactins

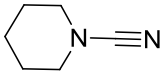
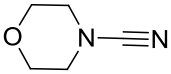
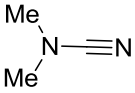
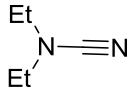
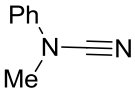
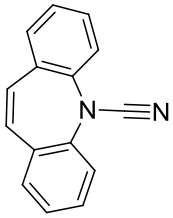
Table 4.3 Cycloaddition of diyne **1c** and various cyanamides



(4.12)

E = CO_2Me

1c cyanamide, **2** **3**

entry	diyne	cyanamide, **2**		reaction time	% isolated yield, **3**
1	**1c**		**2b**	4 h	53, **3e**
2	**1c**		**2c**	5 h	84, **3f**
3	**1c**		**2d**	5 h	82, **3g**
4	**1c**		**2e**	5 h	30, **3h**
5	**1c**		**2f**	5 h	70, **3i**
6	**1c**		**2g**	22 h	69, **3j**

Reaction conditions: 0.4 M diyne, 0.8 M cyanamide, 5 mol % $FeCl_2$, 10 mol % L7, 10 mol % zinc, benzene at 75 °C

References

[1] 2-Aminopyridine bioactive compounds: a) Manna, F.; Chimentia, F.; Bolascoa, A.; Bizzarria, B.; Filippellib, W.; Filippellib, A.; Gagliardic, L. *Eur. J. Med. Chem.* **1999** , *34*, 245−254 b) Perron-Sierra, F.; Dizier, S. D.; Bertrand, M.; Genton, A.; Tuckera, G. C.; Casaraa, P. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 3291–3296. c) Nam, T.; Nara, S. J.; Zagol-Ikapitte, I.; Cooper, T.; Valgimigli, L.; Oates, J. A.; Porter, N. A.; Boutaud, O.; Pratt, D. A. *Org. Biomol. Chem.*, **2009**, *7*, 5103–5112. d) Hagmann, W. K.; Caldwell, C. G.; Chen, P.; Durette, P. L.; Esser, C. K.; Lanza, T. J.; Kopka, I. E.; Guthikonda, R.; Shah, S. K.; MacCoss, M.; Renee M. Chabin, R. M.; Fletcher, D.; Stephan K. Grant, S. K.; Barbara G. Green,B. G.; John L. Humes, J. L.; Theresa M. Kelly,T. M.; Luell, S.; Meurer, D.; Moore, V.; Pacholok, S. G.; Pavia,T.; Williams, H. R.; Wong, K. K. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 1975-1978. e) P. Lechat, S. Tesleff, W. C. Bownan, *Aminopyridines and Similarly Acting Drugs*, Pergamon, Oxford, **1982** f) Goa, K. L.; Brogden, R. N. *Drugs* **1993**, *46*, 428-445.

[2] D'Souza, B. R.; Lane, T. K.; Louie, J. *Org. Lett*. **2011**, *13*, 2936.

[3] Aminopyridines as ligands a) Horie, H.; Koyama, I.; Kurahashi, T.; Matsubara, S. *Chem. Commun.***2011**, *47*, 2658–2660. [b] Daka, P.; Xu, Z.; Alexa, A.; Wang, H. *Chem. Commun.* **2011**, *47*, 224–226. [c] Di Nicola, C.; Effendy, F. Marchetti, C. Nervi, C. Pettinari, W. T. Robinson, A. N. Sobolev, A. H. White, *Dalton Trans* **2010**, *39*, 908–922. [d] J. H. K. Yip, Suwarno, J. J. Vittal, *Inorg. Chem.* **2000**, *39*, 3537–3543 e) Kempte, R.; Brenner, S.; Arndt, P. *Organometallics* **1996**, **15**, 1071. f) Fuhrmann, H.; Brenner, S.; Arndt, P.; Kempe, R. *Inorg. Chem.* **1996**, ***35*** 6742.

[4] Vorbruggen, H.; *Adv. Het. Chem.* **1990**, *49*, 117. b) Ito, Y.; Hamada, Y.; Hirota, M. *Chem. Pharm. Bull*. **1972**, *20*, 2678. b) Katritzky,A. R.; Belyakov, S. A.; Sorochinsky, A. E.; Henderson, S. A.; Chen, J. *J. Org. Chem.* **1997,** *62*, 6210. c) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240. d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, ***65***, 1158–1174.

[5] Bönnemann, H.; W. Brijoux, W.; Brinkmann, R.; Meurers, W. *Helv. Chim. Acta*. **1984**, *67*, 1616.

[6] Heller, B.; Reihsig, J.; Schulz, W.; Oehme, G. *Appl. Organomet. Chem.* **1993**, *7*, 641.

[7] a) Boñaga, L. V. R.; Zhang, H. C.; Moretto, A. F.; Ye, H.; Gauthier, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc*. **2005**, *127*, 3473. b) Zhang, H. C.; Boñaga, L. V. R.; Ye, H.; Derian, C. K.; Damiano, B. P.; Maryanoff, B. E. . *Bioorg. Med. Chem. Lett*. **2007**, *17*, 2863. c) Boñaga, L. V. R.; Zhang, B. E. Maryanoff, B. E. *Chem. Commun.* **2004**, *127*, 3473.

[8] Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 3917.

[9] Stolley, R. M. Maczka, M. T.; Louie, J. *Eur*. *J*. *Org*. *Chem*. **2011**, 3815

[10] Hsieh, J-C.; Cheng, C-H. *Chem*. *Commun*. **2005**, 2459.

[11] a) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 13794. (b) Sylvester, K. T.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8772.

[12] Beesley, M. R.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.*, **1915**, *107*, 1080.

[13] Trost, B. M.; Huang, X. *Chem. Asian J.* **2006**, *1*, 469.